

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

DECAAF II PROTOCOL FIRST VERSION



**Efficacy of DE-MRI-Guided Fibrosis Ablation vs.
Conventional Catheter Ablation of Atrial Fibrillation
(DECAAF II)**

The University of Utah

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PROTOCOL TITLE:

Efficacy of DE-MRI-Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation

Short Title: DECAAF II

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Protocol Version: 2.01

Version Date: April 18, 2016

I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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1 Background and Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of people in the US and around the world. Treating AF continues to be a challenge. Over the last 15 years, catheter based AF ablation procedure has been widely adopted. Approximately 50% of patients treated with catheter ablation present with a persistent type of the arrhythmia. Unfortunately, ablation results in this population have been dismal, not only because of low success rates in suppressing arrhythmias, but also from a healthcare cost point of view. In fact, the long-term success of such a procedure has been reported to be as low as 20%, and patients may need more than two ablation procedures to achieve temporary arrhythmia suppression. The cost of AF ablation among Medicare patients followed for a year after ablation was found to be US\$16,049 ± \$12,536 if ablation was successful versus US\$19,997 ± \$13,958 for failed ablation.¹ A major issue contributing to the low success of catheter ablation is the lack of a protocol to appropriately select patients that would respond to this treatment. Currently, cardiologists base their decision to ablate persistent AF on various comorbidities, a concept that has not been proven successful. With the introduction of AF ablation as a first line therapy option in the recent AHA/ACC/HRS guidelines,² a better and more accurate selection protocol is urgently needed.

There is a strong association between AF and atrial tissue fibrosis. Recently, a novel DE-MRI (Delayed-Enhancement MRI) based imaging modality has been demonstrated to reveal the degree of fibrotic atrial tissue in patients suffering from AF.³⁻⁵ When applied in various studies, including a multi-center study, extent of fibrotic atrial changes was shown to be the strongest independent predictor of a successful treatment in patients undergoing ablation of AF. Moreover, in the multi-center observational study DE-MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF), the strongest independent predictor of successful outcome was the surface area of fibrosis covered by ablation lesions. In fact, the number of encircled pulmonary veins, the most common adopted approach to ablate AF today, did not predict catheter ablation success.⁶

The use of non-invasive ambulatory electrocardiography (ECG) devices including 24-48 hour Holter monitors and 30-day cardiac event monitors have been widely used for the detection of cardiac rhythm abnormalities. The duration of time for rhythm evaluation is key to detect arrhythmias and conduction abnormalities, as number of arrhythmia diagnoses increases with increasing duration of monitoring. The longer duration of monitoring occurs at the expense of patient comfort and patient compliance. Previous FDA-approved devices for standard of care monitoring are limited in the duration of monitoring. At many institutions, it is standard of care to wear a 60-day cardiac event monitor for the detection and evaluation of cardiac arrhythmias in the post-ablation blanking period.

The percentage of asymptomatic recurrences of AF drastically increases after ablation.⁷ Thus, post-procedure devices are necessary for close monitoring and detection

of asymptomatic AF in ablation patients. Compliance with the current cardiac event monitors may be low for many reasons. Electrode intolerance due to skin rashes, irritation and/or breakdown, and the unwillingness for continuous devices to be worn are some known areas of non-compliance.

In this study, a higher level of monitoring will be provided with use of new wireless ECG technologies,⁸⁻¹⁰ specifically, the FDA approved *ECG Check* mobile heart monitor designed by Cardiac DesignsTM. This mobile heart monitor will enable patients to record their heart rhythm anytime and anywhere. The device will automatically analyze the ECG for symptomatic or asymptomatic arrhythmias for the duration of their life as long as it is compatible with their current “smart phone” or tablet computer. This is a patient-owned monitor.

The *ECG Check* is the first FDA-approved over-the-counter ECG monitor that is currently compatible with iPhone[®] 4S and newer, iPad[®] 3 and newer, and approved Android mobile phones. *ECG Check* has also been approved in Europe and has a CE-Mark. This will allow patients to record, store, transfer and analyze single-channel ECG wirelessly through the *ECG Check* app (available for free in the iTunes App Store) and the *ECG Check* Web Center. The information will be uploaded to a protected server through Cardiac DesignsTM.

This proposal is aiming at modifying and improving persistent AF management guidelines by evaluating targeting DE-MRI detected atrial fibrosis during AF ablation and its related effect on procedural outcome.

2 Study Objectives and Endpoint Definition

Primary Objective. To examine the efficacy of targeting atrial fibrosis tissue during an ablation procedure in treating persistent AF.

Results from the DECAAF study show that one of the most important predictors of ablation outcome was the degree of ablation of the fibrotic tissue; the more fibrotic tissue that was overlapped with scar during ablation, the better the outcome. These results were the impetus for the primary objective of DECAAF II. Patients will be randomized to receive conventional pulmonary vein isolation (PVI) ablation or PVI + fibrosis-guided ablation. We will follow patients longitudinally to assess recurrence of persistent atrial arrhythmias (AA) (atrial fibrillation, atrial flutter or atrial tachycardia as defined by recent AHA/ACC/HRS guidelines²). We hypothesize that patients receiving fibrosis-guided ablation in addition to conventional PVI ablation will have fewer AA recurrences than those who receive PVI ablation alone.

We will also examine the efficacy of the fibrosis-guided ablation intervention on a

number of secondary or exploratory outcomes including the individual components of the primary endpoint (atrial fibrillation, atrial flutter and atrial tachycardia), symptomatic atrial arrhythmia, cardiovascular (CV)-related hospitalization, CV-related mortality, quality of life measurements (University of Toronto Atrial Fibrillation Severity Scale (AFSS), and AF burden.

The safety of the two interventions will be evaluated by peri-procedural complications including stroke, pulmonary venous stenosis, bleeding, esophageal injury, cardiac perforation, heart failure, and death.

Our study patients will be followed using the FDA-approved mobile *ECG Check* application. Clinical Center personnel will instruct consented subjects to record ECG data from the *ECG Check* application daily on a smart phone. ECG data will be automatically sent to the central ECG review team. We anticipate that daily ECG follow-up will provide a better-defined endpoint than less frequent follow up assessments as used in previous AF trials.

Definition of Primary Endpoint. The primary endpoint of the study is the recurrence of atrial arrhythmia post-ablation.

The primary endpoint is defined as a non-self-terminating bout of atrial fibrillation, atrial flutter, or atrial tachycardia demonstrated by at least two consecutive, valid ECG tracings occurring within 6 hours up to a maximum of 7 days of each other after the 90-day post-ablation blanking period. The ECG tracings will be obtained primarily from tracings from the *ECG Check* model device, but clinically obtained 12-lead ECG or 24-hour Holter evaluations which indicate atrial arrhythmia will also be included in ascertaining the primary endpoint.

It is difficult to anticipate whether the subject population will have technical difficulty or accessibility issues using the smart phone and tablet devices on a daily basis. Hence, if the patient is unable to continue to use the *ECG Check* mobile device, the patient will be monitored for atrial arrhythmia recurrence using 12-lead ECGs, Holter or other continuous monitoring devices as part of standard of care for the remainder of the patients follow-up period. A 12-lead ECG is required at the end of study assessment period for patients without an ECG assessment within 3 months of the end of follow-up. If a subject undergoes a second ablation procedure during the study period (after the 90-day blanking period) but does not have a documented atrial arrhythmia by the methods described previously, the ablation will also constitute a study endpoint. Ablations occurring within the 90 day blanking period will not be counted as an outcome.

3 Study Design

DECAAF II is a prospective, randomized, multi-center trial of patients with persistent AF and presence of atrial fibrosis. After consenting to participate in the study, the subject will undergo a DE-MRI scan to assess for extent of atrial fibrosis. After verifying adequate quality of the DE-MRI study, subjects will be randomized to one of two study groups to receive conventional PVI ablation (Group 1) or PVI + fibrosis-guided ablation (Group 2), as summarized in Figure 1. In Group 1, PVI ablation will be performed as recommended by the HRS consensus statement² and physicians will be blinded to the pre-ablation MRI fibrosis results. In Group 2, physicians will receive the DE-MRI scan prior to the ablation procedure, will complete conventional PV isolation, and will also target left atrial fibrosis detected by MRI.

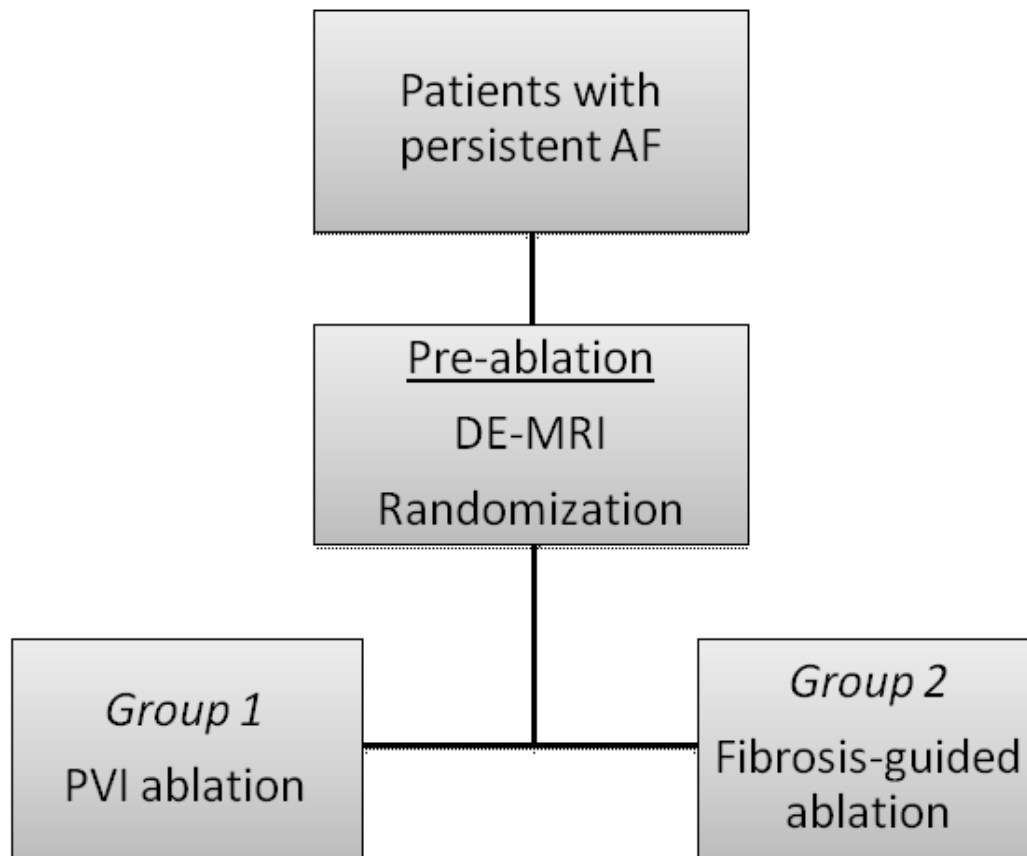


Figure 1: DECAAF-II Study Summary.

Once randomized, the follow-up period for each patient will extend for 18 months following the patient's ablation procedure or until a common administrative censoring date 12 months after the ablation procedure of the final randomized subject, whichever comes first. The trial will be analyzed as an intention-to-treat trial.

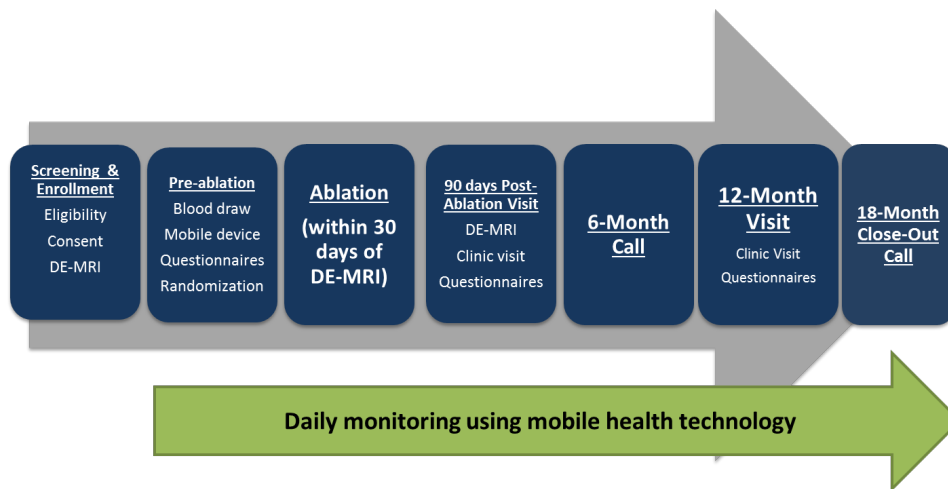


Figure 2: DECAAF-II Workflow

This is an event-driven trial, in which patient enrollment and follow-up will continue until approximately 517 randomized subjects experience the primary endpoint of AA recurrence. Under the assumptions described in Section 6 on page 30, it is anticipated that 888 subjects will be randomized, including 444 assigned to Group 1 and 444 assigned to Group 2. The actual number enrolled and the duration of the follow-up period will be adjusted as necessary to achieve the 517 required events.

Project Enrollment and Follow-up Timeline. The duration of this study is estimated at 3 years.

This will include 9 months allotted for developing materials, IRB approvals, startup activities, and rolling patient enrollment, approximately 12 months for follow-up after the last patient is randomized, and 6 months for close-out activities and manuscript preparation. Our success with DECAAF and the basic inclusion criteria highlight the feasibility of this project to be completed within 3 years. In addition, many of these Clinical Centers participated in DECAAF and presented successful recruitment. A flowchart depicting patient flow through the study is presented in Figure 2.

4 Study Procedures

4.1 Site Selection

All DECAAF II recruiting sites have been or will be pre-screened for eligibility. Sites must have recruitment potential (> 300 persistent AF ablation cases per year) and the proper infrastructure for fibrosis imaging (ability to perform delayed enhancement MRI and Magnetic Resonance Angiography (MRA)). Prior to enrolling subjects, sites must submit sample pre-trial DE-MRI and Magnetic Resonance Angiography (MRA) scans for review and feedback by the imaging team at the University of Utah. Pre-trial scans will be used to identify typical problems during MRI acquisition and provide additional training. Additional scans may be requested if the research site has not demonstrated aptitude for adherence to MR protocol (e.g. timing between contrast injection and late gadolinium enhancement, position of data acquisition during cardiac cycle, duration of data acquisition window, submission of all required image sets, etc.) In addition to the pre-screening and pre-trial process, training materials giving detailed descriptions of MRI acquisition and image submission will be developed and provided to each site. Training sessions will be organized for participating sites.

4.2 Participant Eligibility

Inclusion criteria are:

1. Patients with persistent AF defined as 7 days or more of AF as evidenced by rhythm strips or written documentation; AND
2. Undergoing first AF ablation as per recent HRS consensus document² ; AND
3. Age ≥ 18 years.

Patients are not eligible for DECAAF-II if they have any of the following exclusion criteria:

1. Previous left atrial ablation or any type of valvular surgery; OR
2. Contraindication for DE-MRI with a full dose of contrast agent; OR
3. Contraindication to beta blockers, if necessary, for DE-MRI; OR
4. Women currently pregnant; OR
5. Mental or physical inability to take part in the study; OR
6. Inability to be placed in MRI due to body mass or body habitus; OR
7. Known terminally ill patients; OR
8. Subjects without daily access to a smart phone or tablet compatible with the *ECG Check* application and ability to upload ECG tracings for the entire follow up period.

4.3 Participant Recruitment and Consent

Recruitment Clinical Center staff will approach all potentially eligible patients to participate in the study. If staff decide not to approach specific patients, the reasons for not approaching the subject will be recorded.

Consent If the patient has met the eligibility criteria, the Clinical Center investigator or delegated study staff will approach the patient to explain the study and obtain informed consent from the subject to participate. The investigator or designated staff will provide an explanation of study procedures of the benefits and risks, and the costs and compensation involved with the study. Participants will be given sufficient time to read the consent form and the individual obtaining the informed consent will answer any questions posed by the participant.

4.4 Imaging Protocol

All patients will undergo a DE-MRI within 30 days prior to the ablation procedure using the Marrek DE-MRI protocol (MRI sequence and Image processing software) [8-10]. The purpose of the initial MRI is to quantify the degree of atrial structural remodeling or fibrosis prior to the ablation (Figure 3 on the next page). If a patient has a heart rate ≥ 90 beats per minute, they will be pre-medicated with a beta blocker prior to the MRI in order to obtain optimal images. Images will be sent to Marrek Inc., (Salt Lake City, UT) and will be reviewed for quality by trained technicians using a standard protocol. Images that do not meet quality standards will not be further processed. The site physician may opt to repeat the MRI scan and re-submit it for evaluation. If the image meets quality standards and can be processed, then Marrek will verify that the subject has some proportion of atrial fibrosis (not limited to advanced stage fibrosis). Utah Stages 1-4 (Figure 4 on page 16) will be used to classify patients based on percent fibrosis.

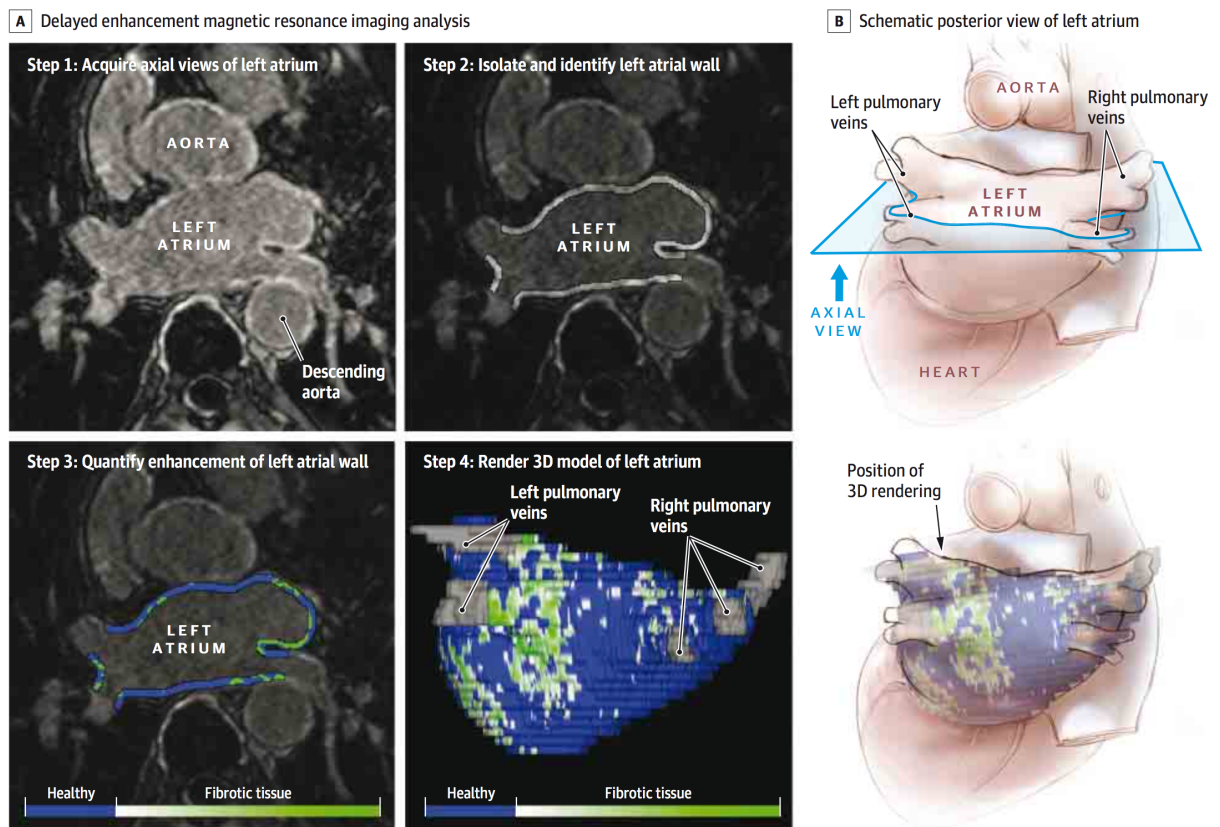


Figure 3: Process for Quantification of Left Atrial Wall Fibrosis.⁶

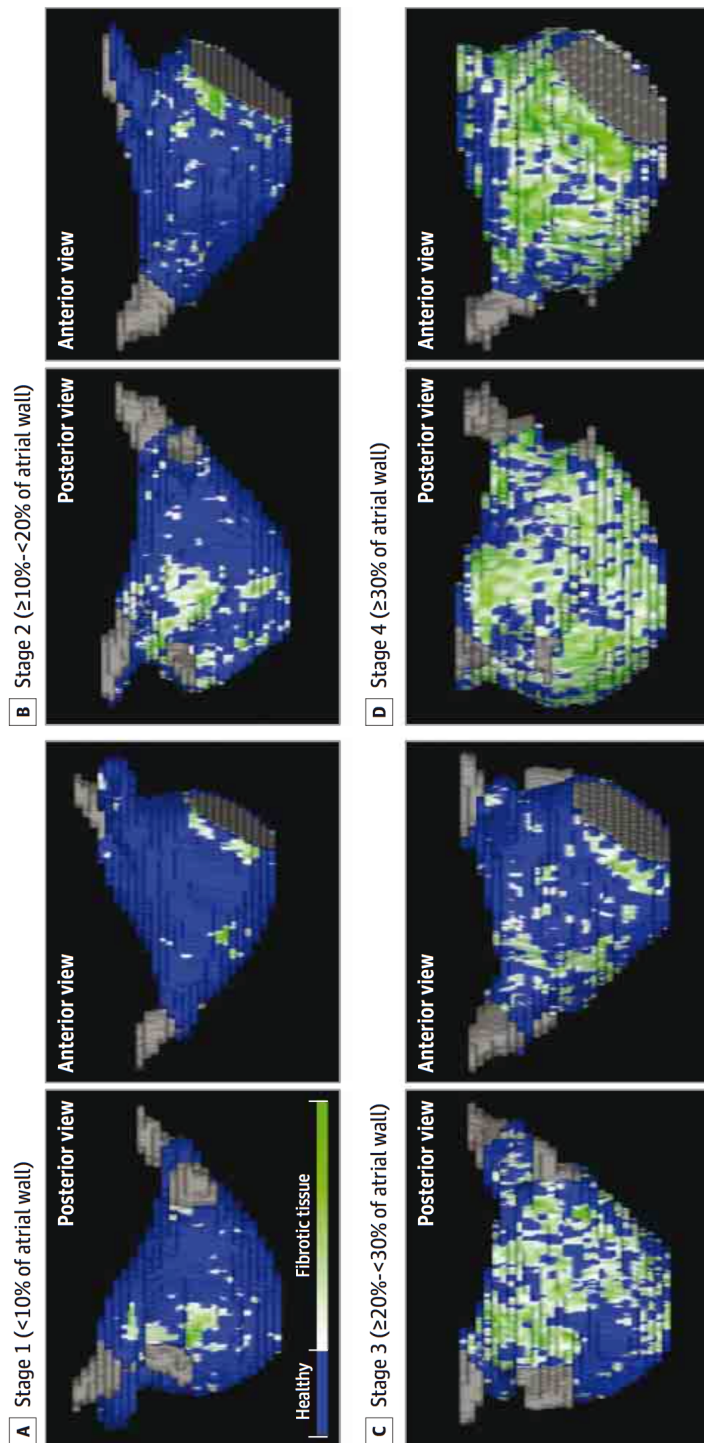


Figure 4: Four Utah Stages of Left Atrial Tissue Fibrosis.⁶

Subjects for whom images are successfully evaluated and scored for fibrosis will then be randomized into the DECAAF-II study. Ablation will be carried out in accordance with the randomized arm of the study. Following ablation, an additional DE-MRI will be obtained at the 90 day follow up to detect and quantify ablation-related scar formation. All MRI scans will be reviewed and analyzed as they arrive from each Clinical Center by Marrek, Inc. for pre- and post-ablation fibrosis and scar quantification respectively. All MRI scans will maintain identifying information to allow the Clinical Center to verify the returned scan matches the subject using their submitted identified information. MRI image processors will be blinded to arm assignment. All images will be retained at the Marrek site for storage and later analysis.

4.5 Randomization

After DE-MRI studies have been evaluated for quality and have been processed and scored for fibrosis, the DCC staff will complete randomization procedures using a web-based randomization service. Randomization will be stratified by Clinical Center and by Utah Stage⁶ (with two Utah stage strata defined by Utah stages I - II, and Utah stages III - IV). For subjects who are randomized to the fibrosis-guided ablation arm (Group 2), DCC will make the processed images available to the investigator at the Clinical Center for use during the ablation procedures. Processed fibrosis images of subjects who are randomized to the PVI ablation group (Group 1) will not be made available to clinicians or site staff. All images will be retained at the Marrek site for storage and later analysis. Clinical investigators will schedule the ablation procedures to occur within approximately 30 days after imaging has been completed.

4.6 Study Biological Samples

Blood samples will be obtained at baseline for each patient. Samples will be analyzed locally for biomarkers of fibrosis and cardiovascular disease including Galectin-3, brain natriuretic peptide (BNP) and C-reactive protein (CRP), respectively. Blood samples will be processed at local sites and results will be entered into the study database. Samples will not be shipped or stored after processing.

4.7 Ablation Protocol

4.7.1 Pulmonary Vein Isolation

All pulmonary veins should be electrically isolated (Figure 5 on the next page) as described by the HRS consensus statement.² The operator will create lesions around the PV antra. Entrance block in all pulmonary veins will be confirmed using standard techniques. Successful ablation is operationally defined as an abolishment of PV electrograms (EGMs). Assessment for the presence of exit block by pacing within the antral lesion set will be at the discretion of the operator.

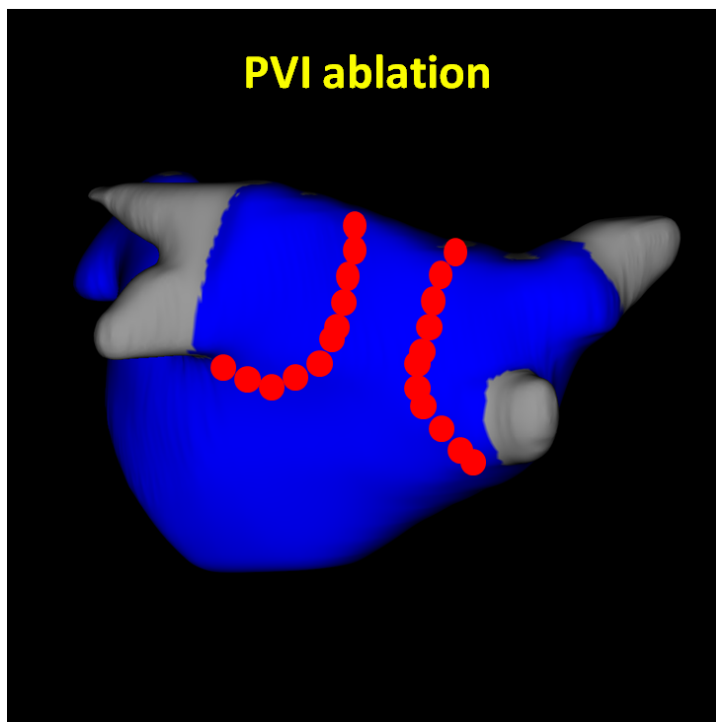


Figure 5: Isolation of the pulmonary vein.

If normal sinus rhythm cannot be restored at the end of the PVI portion of the procedure despite cardioversion in patients randomized to the conventional ablation group (Group 1), the operator may pursue further measures, such as triggering ablation, to eliminate recurrent arrhythmia if needed. The creation of a right atrial cavotricuspid isthmus line is also left at the discretion of the operator.

4.7.2 Cryoballoon Ablation

In case of cryoballoon-based antral PV isolation, it is recommended that a 28mm Arctic Front Advance balloon be used, if possible, to maximize antral ablation when isolating pulmonary veins. While the duration of energy application will be left to the discretion of the operator, we recommend the following general guidelines:

Cryoballoon temperatures below -55°C in the 28mm Arctic Front Advance Cryoballoon, or below -60°C in the 23mm Arctic Front Advance Cryoballoon require termination of energy application.

After a total of 540 seconds of cryoballoon ablation in one pulmonary vein without successful isolation, the physician is encouraged to employ a different strategy (cannulate different vein branch, exchange the catheter for a wire) or employ a different tool (different size cryoballoon, focal cryocatheter, focal RF catheter, etc.).

4.7.3 Phrenic Nerve and Esophageal Monitoring during Cryoablation

When ablating right sided pulmonary veins, phrenic nerve pacing should be performed to ensure safe cryoablation. Additionally, we recommend ensuring the cryoballoon position is as antral as possible to avoid phrenic nerve injury. To allow pacing and monitoring the phrenic nerve, paralytics should not be administered during cryoablation. If phrenic nerve injury occurs, the operator should immediately stop ablation and force balloon deflation.

We recommend continuous esophageal temperature monitoring for cryoballoon ablation as well. As a general guideline, cryoablation should not be performed if esophageal temperatures drop below 25° C.

4.7.4 Fibrosis-Guided Ablation

For subjects randomized to the fibrosis-guided ablation group (Group 2), processed DE-MRI images will be merged with the 3D mapping system used at the Clinical Center. All patients will undergo the previously described pulmonary vein isolation procedure (PVI). Pulmonary vein entrance block at the end of the ablation procedure should be confirmed and is defined as loss of pulmonary vein potentials using standard techniques.

After PVI and PV entrance block have been confirmed, fibrosis-guided ablation will ensue. The operator will encircle by ablating at the perimeter of the fibrosis and ensure loss of capture in the fibrotic isolated area at 10 milliamp stimulation, and/or completely cover all fibrotic areas with ablation lesions. The tagged ablation lesions should confirm encircling and/or covering of the entire contiguous fibrotic areas indicated by the mapping system. Ablation to the fibrotic areas should be performed as per the operator's standard point lesion energy delivery strategy. It is suggested that a minimum of 8-10 s (and if available 10 g of force) lesions should be delivered. It is recommended that energy delivery (power and temperature) should be adjusted as needed when ablating within the posterior wall region over the region of the esophagus. The operator may connect 2 neighboring fibrotic areas or anchor fibrotic area to anatomic structure such as the isolated PV or valve annuli to avoid creating slow conduction zones or unanchored islands of fibrosis that might be deemed to be potentially arrhythmogenic.

Guidelines for fibrosis-guided ablation are shown in [Figure 6 on the following page](#) for dense localized fibrosis, and in [Figure 7 on page 21](#) for extensive posterior or anterior wall fibrosis.

In case of cryoballoon ablation, further ablation to cover areas of atrial fibrosis should be guided by the 3D mapping system, intracardiac echocardiography, or fluoroscopic landmark. The duration of freezing targeting fibrotic areas will be left to the discretion of the operator.

If the normal sinus rhythm cannot be restored after PVI and ablation of fibrotic areas followed by cardioversion in patients randomized to the fibrosis-guided ablation group

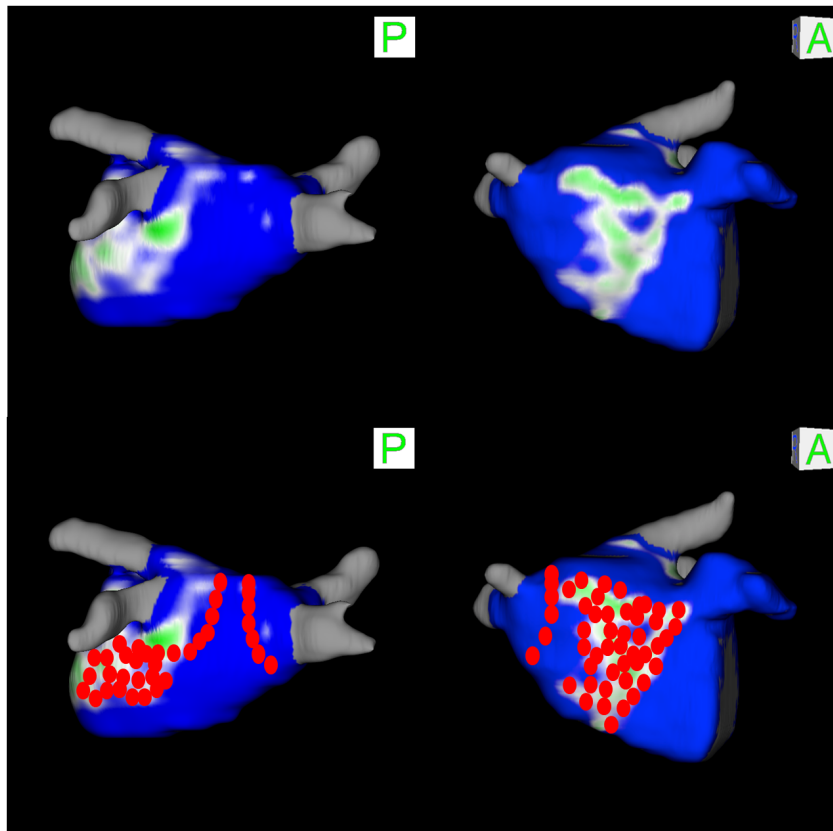


Figure 6: Ablation strategy for dense localized fibrosis.

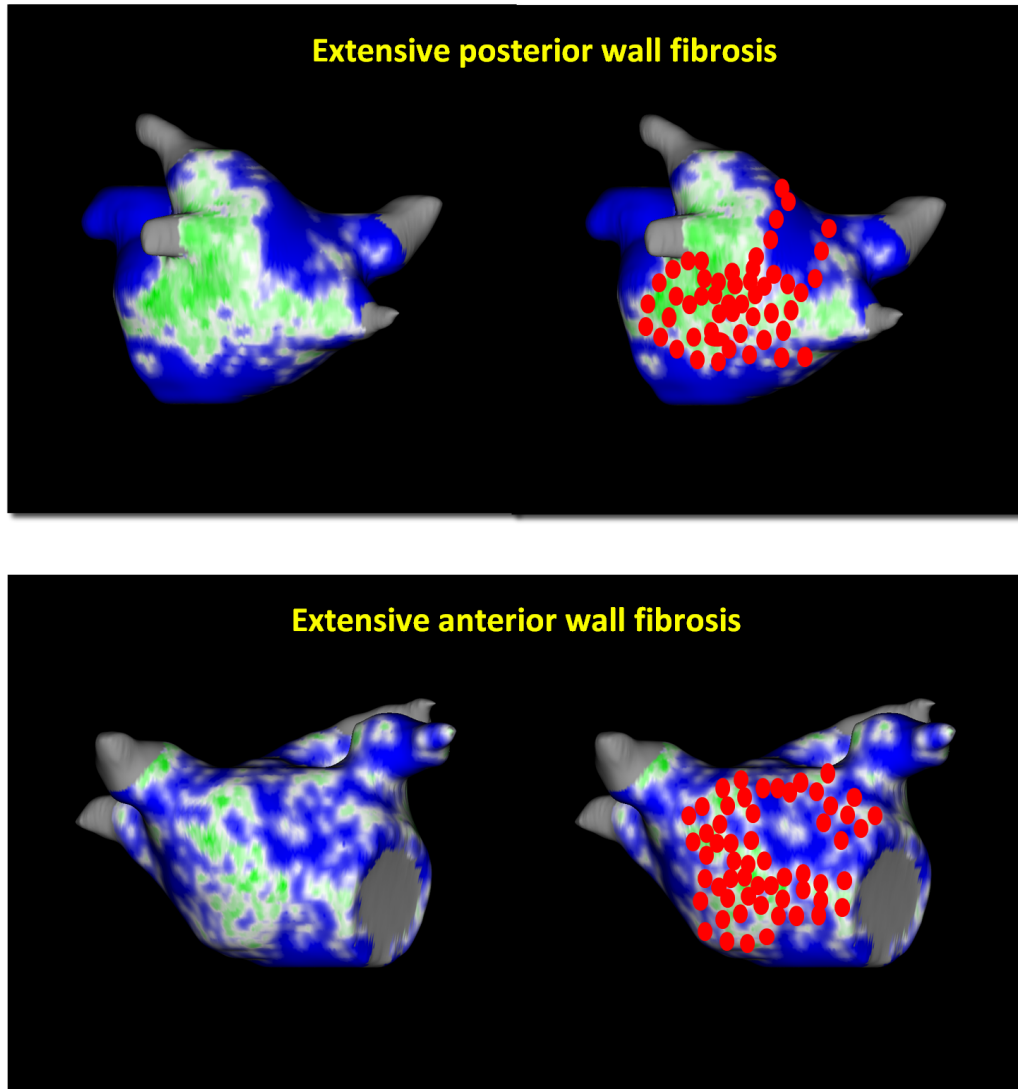


Figure 7: Ablation strategy for extensive fibrosis.

(Group 2), the operator may to pursue further measures to eliminate recurrent arrhythmia, as described above for the conventional ablation group (Group 1).

To assess ablation procedure protocol compliance, a select subset of cases from both treatment groups will be reviewed using a standardized assessment process. The assessments will then be evaluated by the Steering Committee. Procedure reports and relevant data will be reviewed to ensure that the operator targeted appropriate areas based on the patients randomized treatment assignment.

4.7.5 Anti-Arrhythmic Drugs

Clinicians are encouraged to discontinue the use of anti-arrhythmic drugs after the 90-day blanking period.

4.7.6 Repeat Ablation Procedures

In accordance with current standard of care, repeat ablations are discouraged during the blanking period. Following the 90 day blanking period, repeat ablations should be performed using a method preferred by the operator.

4.7.7 Clinical Follow-up

Clinical Center staff will continue post-procedural care following standard of care procedures. Patients will be scheduled for a follow up visit in the 4th month after ablation (between 90 and 120 days post ablation). At this visit, a post-ablation DE-MRI will be completed to document post-ablation fibrosis coverage and to detect and quantify ablation-related scar formation. Images that do not meet quality standards will not be processed and will be returned to the site. If the post-ablation MRI scan does not meet quality standards, the site physician must repeat the post-ablation MRI scan and re-submit it for evaluation.

5 Study Data

The Clinical Center investigator or delegated study staff will screen subjects for eligibility. For subjects that meet inclusion criteria, the Clinical Center staff will enter the specific exclusion criteria into the database. If the patient is ineligible at this point, no further data will be recorded and the patient will not be approached.

5.1 Pre-Treatment Data

Pertinent review of systems findings will be recorded and this historical information will be used to determine whether subsequent events are different from baseline. This is relevant to adverse event reporting.

5.2 Ablation Procedure Data

Ablation procedure data from the 3D mapping system used the ablation procedure at the study center (e.g. CARTO, Biosense Webster, Ensite NavX, St. Jude Medical, or Rhythmia, Boston Scientific) will be exported and backed up following the procedure and submitted on a regular basis to the DCC for storage and analysis. Sites will use their existing mapping systems during the study. Due to the volume of sites and patients, mapping systems, CARTO and Ensite Navx, will be utilized in at least 50 study patients.

5.3 Study Data Elements

We will be collecting data from medical records including demographic information, medications, medical history, lab results, and other relevant clinical data. In addition, we will be collecting data acquired from ECG, MRI, and electrophysiological output devices, reported data such as hospitalizations, adverse events, illnesses, medication changes, clinic visits, and subjective measurements such as quality of life and symptoms of illness.

5.4 ECG Data

5.4.1 ECG Data Collection using *ECG Check* and Other Available Studies

Enrolled patients will transmit *ECG Check* data regularly to the ECG analysis center, which has the capability to read, interpret and store ECG tracings. At the time of enrollment, the Clinical Center personnel will assign each patient a unique identifier. This identifier will be entered into the *ECG Check* device at the participating site by research personnel so that the patient's ECG transmissions will always be associated with their study ID. Patients will be instructed to record their ECG daily, and transmissions of the *ECG Check* data will be sent automatically to the ECG analysis center. ECGs will be reviewed and rhythms will be identified by trained experts blinded to treatment arm assignment. The ECG analysis center will send data regularly to the DCC for data analysis and storage purposes.

If *ECG Check* data are not transmitted on a given day, an alert will be automatically sent to the patient's smart phone to remind the patient to resume *ECG Check* tracings. If *ECG Check* tracings are repeatedly missed, the Clinical Center staff will be responsible for contacting the patient to remind them of the importance of sending the daily *ECG Check* tracing. Clinical staff must document their attempts to contact the patient if *ECG Check* tracings are not received.

Any available data from 12-lead ECGs, Holter monitors, or other continuous monitoring devices will be transmitted to the DCC for inclusion in the study database. These types of studies will not be transmitted to the ECG analysis center for review; rather, such studies obtained in association with a study outcome will be read by an independent expert to verify the presence of atrial arrhythmia. This expert will be blinded to study

arm. In cases where a Holter or other continuous heart monitoring device was done as part of standard of care site staff will upload the summary report to the study database.

5.4.2 Definition of Study Outcome using *ECG Check* and Other Available Studies

The study outcome is formally defined by at least two consecutive, valid ECG tracings indicating an atrial arrhythmia (AA)(atrial fibrillation, atrial flutter or atrial tachycardia). Both tracings must be completed after the 90-day blanking period, and the two consecutive tracings demonstrating an atrial arrhythmia must be recorded between 6 hours and 7 days of each other. If an *ECG Check* tracing demonstrates a non-self-terminating bout of an atrial arrhythmia (AA), the DCC systems will send a notification to the Clinical Center indicating that an atrial arrhythmia has been observed. If a second, consecutive *ECG Check* reading also demonstrates an atrial arrhythmia 6 hours or up to 7 days after the first recording, the DCC system will notify the Clinical Center that the studys primary AA recurrence outcome has been reached.

It is expected that the majority of enrolled patients who reach the primary study outcome will do so due to two consecutive *ECG Check* tracings demonstrating AA as above. However, these same criteria, requiring demonstrated atrial arrhythmia occurrences no less than 6 hours and no more than 7 days apart, will also be applied to any readings obtained from 12-lead ECGs, Holter monitors, or other continuous recording devices. In some instances, this may mean that the study endpoint is achieved from a single monitoring study lasting more than 6 hours. It is also possible that a patient may achieve the study outcome from multiple sources (e.g., a single *ECG Check* reading of AA followed by a finding of AA from a 12-lead ECG performed 6 hours to 7 days later).

In the possible scenario where a repeat ablation is performed after the 90-day blanking period, but there is no AA recurrence demonstrated by an ECG measure (e.g. 12-lead ECG, *ECG Check* or Holter), AA recurrence will be inferred for the purposes of the primary study analysis and assigned to the date of the repeat ablation.

The DCC will send notification of the subject having met the primary study outcome to the Clinical Center. The Clinical Center clinician may follow up with the patient based on local standard of care or clinician judgment.

5.5 Symptom Reporting and Quality of Life

At baseline, 3 month, and 12 month clinic visits, participants will complete the University of Toronto AFSS¹¹ and SF-36 questionnaires . Symptom reporting will occur using the *ECG Check* application. Every other week, symptom questions will appear on the *ECG Check* phone application and subjects will indicate the answers to questions regarding

AA-related symptoms using their smart phone or tablet. Responses to these questions will be transmitted securely to the DCC. The clinical center will receive a notification if the patient marked a positive answer to the symptom question or to hospitalization. Clinical center staff may contact subjects based on symptom report if clinically warranted. These will not be considered adverse events; however if a subject presents to the clinic with these symptoms and receives clinical evaluation, treatment or hospitalization, and if the symptom is not pre-existing, then clinical sites will report these as adverse events, as described in Section 9.2 on page 46 .

5.6 Database Lock

After the last subject accrual and follow-up visit, the database will not be able to be locked until all data queries have been resolved. Quantitative data will be examined statistically, prior to locking the database. When all such verifications have been completed, the database will be locked prior to undertaking the final data analyses for the study.

6 Statistical Analyses and Power

6.1 Analysis Populations

Randomized Study Population. The randomized study population consists of all randomized patients, irrespective of whether the patient receives an ablation procedure or remains in the trial at the close of the blanking period.

Modified Randomized Study Population. The modified randomized study population consists of all randomized patients who receive an ablation procedure, irrespective of whether the patient remains in the trial at the end of the blanking period.

Safety Population. The safety population consists of all randomized patients who receive an ablation procedure.

Modified Intent-to-Treat Population. The modified intent-to-treat population consists of all randomized patients who receive an ablation procedure and remain in follow-up at the close of the 90-day blanking period.

Unless indicated otherwise, all statistical analyses of efficacy outcomes will be performed in the modified intent-to-treat population and all analyses of safety outcomes will be carried out in the safety population.

6.2 Descriptive Analyses of Baseline Characteristics

Descriptive summaries of baseline clinical and demographic characteristics will be provided by randomized treatment assignment for each analysis population. Baseline characteristics

will also be summarized by randomized group in the modified intent-to-treat population for each clinical center and region. In the event that substantial imbalances in particular factors between the randomized treatment groups are detected, sensitivity analyses will be performed after adding these factors as covariates to the Cox regression used for subsequent analyses.

6.3 Primary Analysis of Atrial Arrhythmia (AA) Recurrence

The primary efficacy analysis will be performed in the modified intent-to-treat population using a stratified log-rank test to compare the time to the first AA recurrence after the blanking period between the randomized treatment groups. The log rank test will be stratified by Utah Stage (separate strata for Utah stages I - II, and III - IV). Follow-up will be censored at loss-to-follow-up or death. The primary analysis will be performed with a 2-sided significance level (α) of 0.05.

An associated Cox proportional hazard regression analysis with the same stratification factors will be performed to estimate the hazard ratio between the fibrosis guided ablation and conventional ablation groups with its 95% confidence interval. The possibility that the hazard ratio for treatment assignment varies over the follow-up period (non-proportional hazards) will be investigated by smoothed Schoenfeld residual plots and by performing time-dependent Cox regressions including interaction terms between treatment assignment and follow-up time.^{12, 13} Cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group using a competing risk framework.^{14, 15}

6.4 Components of AA Recurrence

The frequencies and proportions of patients experiencing each of three components of the primary AA outcome:

- atrial fibrillation
- atrial flutter
- atrial tachycardia

will be tabulated by treatment group. As in the primary analysis, only events occurring after the end of the blanking period will be counted in these analyses. Cox regression analyses in which the baseline hazard function is stratified by Utah stage and region will be used to obtain estimates of cause-specific hazard ratios and associated 95% confidence intervals to compare the three components of the primary outcome between the randomized treatment groups. Cumulative incidence curves will be constructed for each of the three components and death under a competing risk framework.^{14, 15} The same analyses will also be performed for symptomatic AA and for symptomatic AA requiring treatment. Because these analyses of the components of the primary endpoint are explanatory, no

adjustment for multiple comparisons will be performed.

6.5 Subgroup Analyses of AA Recurrence

Stratified log-rank tests and Cox-regressions similar to those described for the primary analysis will be used to compare the fibrosis guided ablation and conventional interventions in subgroups defined by baseline fibrosis $<$ or \geq 20%. The log-rank test and Cox regression in the fibrosis $<$ 20% subgroup will be stratified by Utah Stages I and II, while the analyses of the fibrosis \geq 20% subgroup will be stratified by Utah Stages III and IV. These analyses will be repeated for the three components of the primary outcome.

6.6 Within-Treatment Group Analyses of AA Recurrence

Cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group separately for each of the four Utah stages in order to estimate the proportions of subjects reaching these events by 1 year and by 18 months within each Utah stage. Separate Cox regression models using cubic splines for percent fibrosis will be used to relate the hazard for AA recurrence to the pre-ablation percent fibrosis within each randomized group. Similar Cox regressions with cubic splines will be performed within each randomized group to relate the hazard for AA recurrence to the percentage of fibrosis which is covered by the ablation procedure.

6.7 Main Secondary Efficacy Outcome

Quality of life as measured by the Toronto Atrial Fibrillation Burden Scale will be treated as the main secondary efficacy outcome. The main secondary analyses will estimate the effect of the treatment on the mean Toronto Atrial Fibrillation Burden Scale at months 3 and 12 under a mixed effects model in which the baseline Toronto Atrial Fibrillation Burden Scale, visit month (treated as a categorical variable) and the interaction between treatment and visit month are included as fixed effects. An unstructured covariance model will be used to account for serial correlation across the follow-up visits. The main contrast for testing the effect of the treatment will compare the adjusted mean Toronto Atrial Fibrillation Burden Scale at month 12 between the guided ablation and usual care groups. A secondary contrast will compare the adjusted mean Toronto scores at months 3 and 12 between the guided ablation and usual care groups.

6.8 Additional Efficacy Outcomes

Stratified log-rank tests and associated Cox-regressions will also be used to compare initial occurrences of

- a composite outcome including AA recurrence and prescription of an anti-arrhythmic medication,

- stroke,
- cardiovascular hospitalization,
- a repeat ablation,
- AA recurrence following repeat ablation

between the randomized treatment groups. The analysis of repeat ablations will evaluate the time from the end of the blanking period to the first ablation performed after the close of the blanking period. The analysis of AA recurrence following repeat ablation will evaluate the time from the end of the blanking period to the first AA recurrence following the first repeat ablation. If the patient has an AA recurrence after the blanking period but does not have a repeat ablation, the outcome for this analysis will be defined as the initial AA recurrence after the blanking period.

Mixed effects analyses similar to those described for the Toronto scores will be performed to compare the physical and mental composite scores from the SF-36 between the randomized group at months 3 and 12, with primary emphasis given to the month-12 comparison.

The proportions of positive responses to the 5 questions asked every other week pertaining to chest pain, shortness of breath, heart racing, dizziness, and syncope will be displayed graphically along with associated exact binomial 95% confidence intervals by follow-up week and treatment group. The mean proportions of positive responses over the full follow-up period will be compared between the fibrosis-guided ablation group and the usual care group using generalized estimating equations with a working identity covariance matrix, with covariate adjustment for the baseline responses.¹⁶ The Huber sandwich estimator will be used to compute robust standard errors for statistical inferences.

AA burden will be estimated for each month of follow-up for each subject as a time-weighted average of the proportion of *ECG Check* readings during that follow-up month which indicate the presence of AA. Generalized estimating equations with stabilized inverse probability of censoring weights to account for early loss-to-follow-up will be used to compare these proportions between the randomized treatment groups.

6.9 Safety Outcomes

The primary safety *composite* outcome is defined by occurrence of one or more of the following events during the 30 day period following the ablation procedure:

- stroke
- pulmonary vein stenosis,
- bleeding,
- heart failure and
- death.

Additional safety outcomes include each of the individual components of the primary safety composite as well as the occurrence of cardiac perforation or esophageal injury within 30 days of the ablation procedure. The primary safety composite and the other safety outcomes will be compared between the randomized treatment groups among patients in the safety population using Fisher exact tests.

The above endpoints as well as all serious adverse events will be monitored and documented throughout the follow-up period. Additionally, clinical sites will document all cardiovascular, cerebrovascular, and gastrointestinal adverse events (including non-serious adverse events in these categories) which are recorded in the patient record or reported at study visits. The distributions of the duration of the ablation procedure and fluoroscopy time will also be summarized by randomized group. The distributions of the duration of the ablation procedure and fluoroscopy time will also be summarized by randomized group.

Frequencies and proportions of the safety population experiencing each of safety endpoint will also be tabulated in the safety population by randomized group over the full follow-up period, including both the blanking period and the further follow-up after the close of the blanking period. The rates of each safety endpoint (potentially including repeat events in the same patients), expressed as the number of events per 100 patient-years of follow-up, will also be summarized over the full follow-up period.

6.10 Capability of Mobile Health Technology to Follow Patients After Ablation

The number of days with valid *ECG Check* readings will be tabulated weekly for each patient and summarized graphically by treatment group for each week throughout the follow-up period. The proportions of subjects with at least one valid *ECG Check* reading during each week of follow-up will be tabulated and graphically displayed. The largest gap (in days) between successive valid *ECG Check* recordings during the follow-up period will also be computed for each subject and summarized by randomized group.

6.11 Statistical Power and Sample Size

Using an event-driven design, the trial will proceed until a total of approximately 517 arrhythmia recurrence events are recorded to provide 90% power with a 2-sided Type 1 error of 0.05 to detect a reduction in the hazard rate for arrhythmia recurrence by 25% in the fibrosis guided ablation group compared to the conventional ablation group. The sample size required to achieve 517 events depends heavily on the underlying event rate of AA recurrence in the conventional arm. Table 1 on the next page summarizes estimates of the fraction of patients reaching AA recurrence provided in recent studies of patients with persistent AF. As will be the case in DECAAF II, the DECAAF I and Scherr et al studies included general populations of persistent AF patients,^{6, 17} while the STAR AF

study was restricted to persistent AF patients with ≤ 3 years of sustained AF and atrial diameter < 60 mm [16]. Daily monitoring by the *EKG Check* is expected to provide a higher event rate than observed in DECAAF I and in Scherr et al, in which monitoring was performed at a limited number of follow-up visits, and the inclusion of subjects with of sustained AF ≥ 3 years and atrial diameter ≥ 60 mm may lead to a higher event rate than observed in the STAR AF trial.¹⁸ Based on these considerations, the 1-year atrial arrhythmia recurrence probability is projected to fall between 0.50 and 0.70, and a 1-year atrial arrhythmia recurrence probability of 0.60 is used for initial projections of the required sample size.

Table 1: Estimated recurrence rates for persistent atrial fibrillation.

Study	Sample Size	Monitoring	Specific outcome	Reported Event Rate	Estimated Proportion of Subjects with Events by 1 year
DECAAF I ⁶	75	Holters and 12 leads at 3 mos, 6 mos and 1 yr	AA recurrence	36.4% at day 325 after blanking period	36.4% (applies day 325 event rate to 9 months)
STAR AF ¹⁸ (All 3 treatment arms)	589	Holters and 12 leads at 3,6,12, and 18 months + Weekly trans-telephonic monitoring	AA recurrence	59.9% at 18 months after ablation not counting use of anti-arrhythmic drugs	51.3%*
			AA recurrence or use of anti-arrhythmic drugs	67.9% at 18 months after ablation with arrhythmia recurrence of use of anti-arrhythmic drugs	59.3%*
STAR AF ¹⁸ (Isolation Alone arm only)	67	Holters and 12 leads at 3,6,12, and 18 months + Weekly trans-telephonic monitoring	AA recurrence	50.8% at 18 months after ablation not counting use of anti-arrhythmic drugs	42.8%*
			AA recurrence or use of anti-arrhythmic drugs	59.0% at 18 months after ablation with arrhythmia recurrence of use of anti-arrhythmic drugs	50.4%*
Scherr et al ¹⁷	150	Holters at 1,3,6,12 months	AA recurrence	64.7% 1 year after ablation	64.70%

* Assumes 60% lower event rate after year 1 than during year 1.

A total sample size of 888 randomized patients is expected to provide the required 517 events under the following assumptions:

- 60% of conventional ablation subjects have AA recurrence by 1 year after ablation (9 months after the end of the blanking period), and 68% have AA recurrence by 18 months after ablation; and
- the AA recurrence event rate will be reduced by 25% in the fibrosis-guided ablation group compared to the conventional ablation group; and

- 3% of subjects are lost during the 90 day blanking period, and 0.45% of subjects subsequently die or are lost to follow-up per month; and
- patients are accrued uniformly over a 12-month accrual period, this being a conservative estimate; and
- follow-up will extend for 18 months following each patient's ablation procedure or until a common administrative censoring date 12 months after the ablation procedure of the final randomized subject, whichever comes first; and
- two interim analyses are performed after approximately 1/3 and 2/3 of the total projected number of events have been observed using an O'Brien-Fleming type stopping boundary.

Interim assessments of the actual accrual and event rate (blinded to treatment assignment) will be used to modify the actual number of randomized patients above or below 888 patients in order to assure that approximately 517 AA recurrence events are observed. The projected number of required patients would be 744 if the AA recurrence percentage is 70% at 1 year and 1061 if the AA recurrence percentage is 50% at 1 year.

6.12 Interim Analyses

Interim analyses will be carried out after approximately 1/3 and after approximately 2/3 of the projected total number of events have occurred to guide the Data Safety and Monitoring Board in determining if the trial should be terminated early either due to clear evidence of a benefit of one of the treatment goals, or to a near-0 conditional probability (futility) that the trial would be able to establish a benefit of one of the interventions on scheduled completion. Reports will include adverse events, unanticipated problems, and study outcome results. The α spending function approach of Lan and DeMets will be applied under an approximate O'Brien-Fleming boundary to guide early termination due to efficacy. Futility will be assessed using conditional power calculations.

7 Data Management

7.1 Clinical Sites

Study data may be recorded on paper forms, or directly entered into the electronic data capture (EDC) system. Paper forms will be retained at the Clinical Center and data will be entered by Clinical Center staff into the EDC system provided by the DCC at the University of Utah School of Medicine. The investigator at each participating Clinical Center is responsible for all aspects of study implementation, including MRI procedures, ablation procedures, subject follow-up, collection of accurate study data, and correct entry of the data into the data collection system. These tasks may be specifically delegated to other individuals at the Clinical Center, but the Clinical Center investigator is responsible to supervise all aspects of the study, and is responsible to assure that all staff involved in this study are adequately trained to perform the delegated tasks.

7.2 DECAAF-II Data Coordinating Center

Clinical data will be entered and securely stored using a secured web-based EDC and database at the DECAAF-II Data Coordinating Center (DCC) which will be at the University of Utah Department of Pediatrics.

7.2.1 Facility, Hardware, Storage, Data Backup and System Availability

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center completed in 2013. The data center facility supports more than 1200 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 95% of its environment. The virtual environment consists of more than 160 virtual servers and nearly 20 physical servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware or software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages over 50 terabytes of data. The storage solution consists of Dell's EqualLogic PS Series Storage system for providing a virtualized storage area network (SAN). Some of the benefits that are realized through this technology are:

- storage architecture will no longer be a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of SAN disk will be much easier; and most important,
- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. Our storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

Our information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

7.2.2 Security, Support, Encryption and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the SSL protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run

against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2008 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

The European Union (EU) has stringent regulations regarding data and patient protection. The Data Coordinating Center (DCC) and the European sites will abide by these regulations.

7.3 Major DCC Software Resources

Extensive software resources are available to support the DECAAF-II study. These include support for electronic collaboration using eRoomTM, database and data warehouse software, clinical trial software, Web server software, our query management system, statistical software, videoconference software, on-line training software, and extensive reporting capabilities.

7.3.1 Electronic Collaboration Support: eRoomTM

We use eRoomTM to provide a “digital office” to support secure, confidential communication and collaboration among multiple users. The software is Web-based and uses an office metaphor of rooms that may contain folders, documents, task lists, calendars, and task oriented databases (Figure 8 on the facing page). The software is highly secure, and management of documents is very intuitive.

The user can drag documents to and from their own desktop directly into the eRoomTM system. The system is optimized to integrate with standard office applications. We have used eRoomTM to support all aspects of coordination since inception of our first

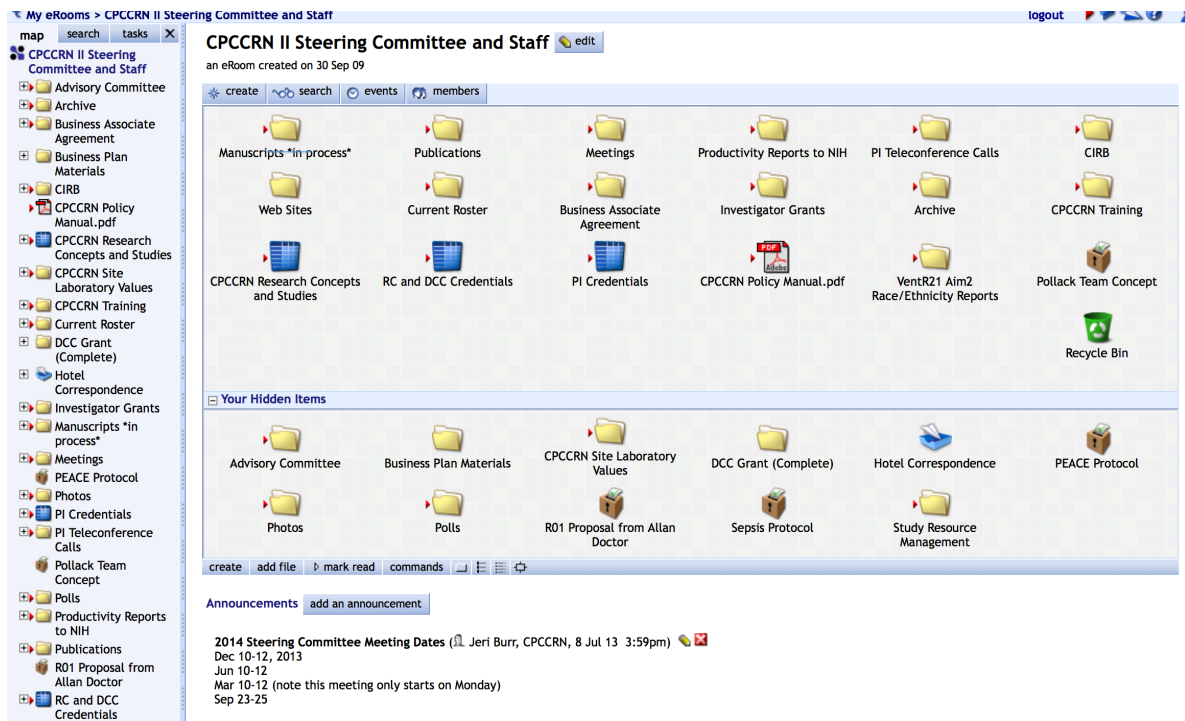


Figure 8: Example Network Steering Committee eRoom

research network, including coordination of the Steering Committee and subcommittees, preparation of protocols, grants, manuscript preparation and publication, tracking IRB applications and approvals, and storage of scanned regulatory documents. For example, in Figure 9, each underlined entry links directly to a scanned copy of the IRB document, providing the DCC and the funding agency with thorough documentation and continuous access to required documents.

The eRoomTM is also used for organization of materials for individual research projects

CRISIS IRB Documents [edit](#)

a database created by [David Nilson](#) on 12 Jan 07

[new entry](#) [show search](#) (all 8 entries shown)

Below is a list of the CPCCRN Sites and their IRB status.

	Site	Original Approval	Amend v1.13	Amend v1.14	Amend v1.15	#1 Renewal	Amend v1
	Seattle Children's Hospital	11 Apr 08 (v1.14)	N/A	N/A	11 Apr 08	09 Apr 09	11 Apr 08
	Children's Hospital of Los Angeles	19 Jun 08 (v1.14)	N/A	N/A	19 Jun 08	15 Apr 09	19 Jun 08
	Arkansas Children's Hospital	07 Nov 07 (v1.10)	07 Nov 07	07 Nov 07	10 Apr 08	01 Oct 08	01 Oct 08
	Children's Hospital of Michigan	21 Mar 08 (v1.13)	N/A	21 Mar 08	21 Mar 08	12 Mar 09	21 Mar 08
	University of Pittsburgh Medical Center	14 Mar 08 (v1.14)	N/A	N/A	14 Mar 08	20 Aug 08	14 Mar 08
	Children's National Medical Center	01 Apr 08 (v1.13)	N/A	01 Apr 08	01 Apr 08	06 Feb 09	01 Apr 08
	University of California Los Angeles	21 Aug 08 (v1.13)	N/A	N/A	21 Aug 08	05 Mar 09	05 Mar 09

Figure 9: Managing scanned documents with eRoomTM

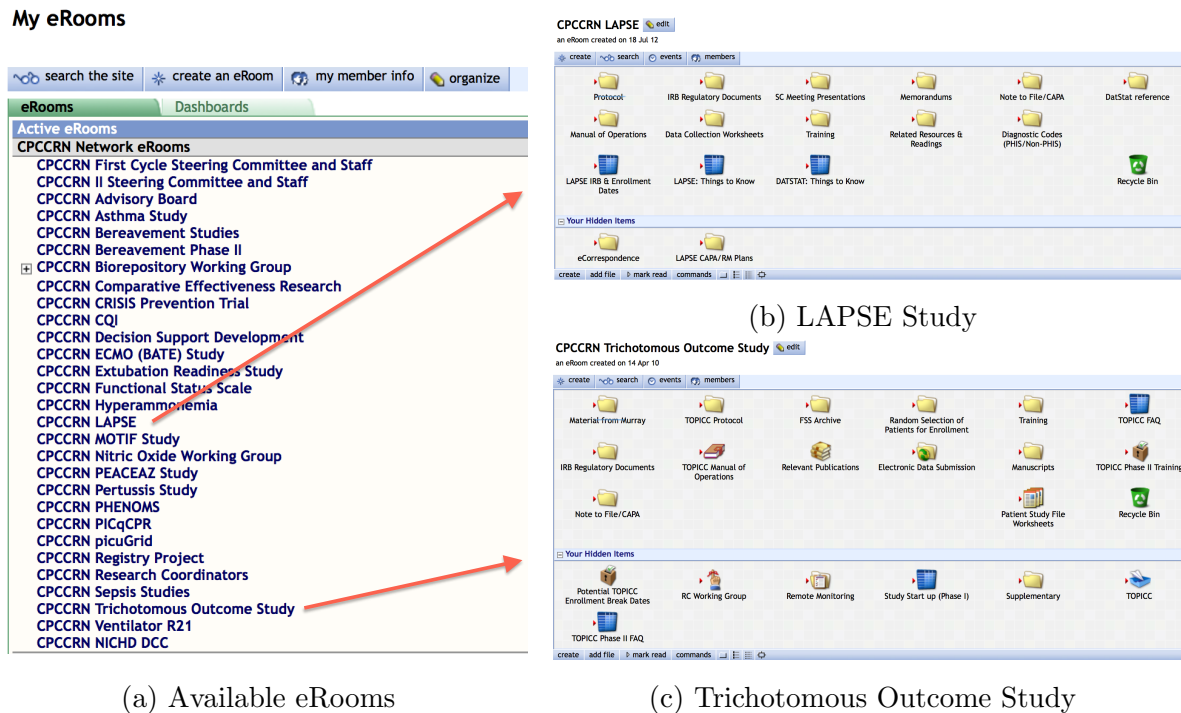


Figure 10: Example network study eRooms.

(Figure 10). When the user logs into the system, a listing of eRooms available to that user is displayed (Figure 10a), from which the user can click on the selected study eRoom (examples are shown for the LAPSE (Figure 10b) and Trichotomous Outcome (Figure 10c) studies that are being conducted in one of our NIH funded networks). This provides significant efficiency, as it eliminates printing and mailing of large amounts of paper documents. The system allows us to automatically notify study personnel of protocol changes, updates to Manuals of Operation, and important communications within the any individual project. Investigator and research coordinator acceptance of eRoomTM has been enthusiastic and uniform in the eight current networks that we support.

7.3.2 Database Software

We use Microsoft SQL Server as our primary relational database engine, and have extensive experience (over 20 years) accessing the database from SASTM, Microsoft Access, PHP, Python, Perl, Java, and JavaScript. Microsoft SQL Server provides sophisticated security facilities. We support a number of large databases (tens of millions of records) used for research in the Intermountain Injury Control Resource Center (IICRC), in addition to supporting the network studies. The databases are not directly accessible from outside the offices of the DCC unless a VPN connection is established.

Several of our networks have implemented registries. To enable investigator access to these registries, we create an On-Line Analytical Processing (OLAP) data warehouse

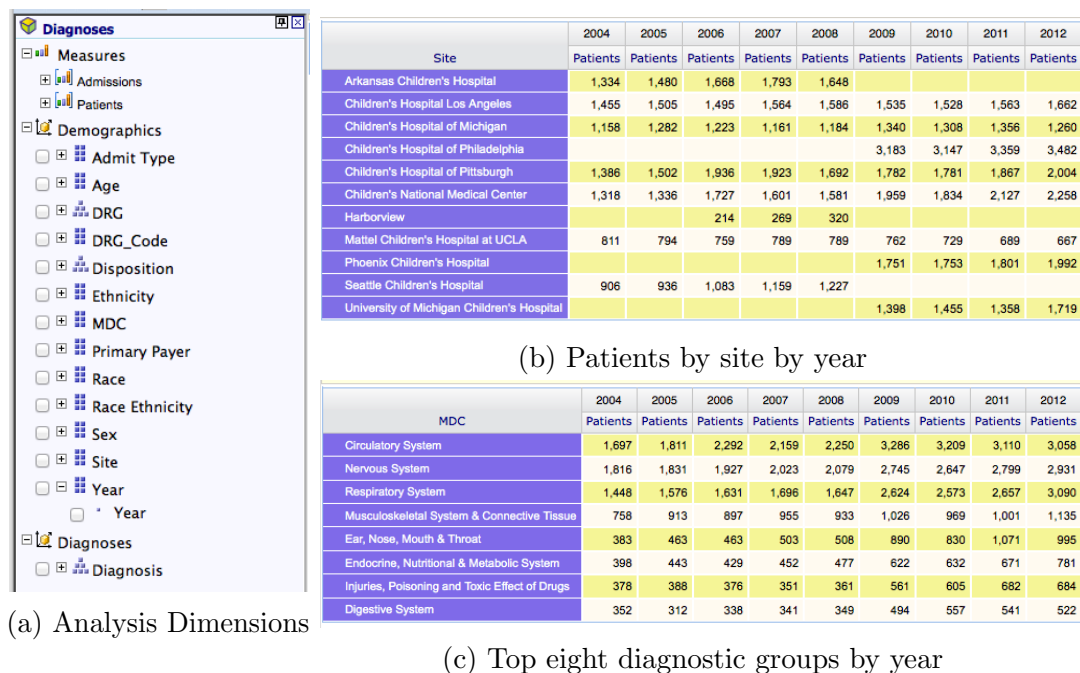


Figure 11: Network Registry data warehouse.

that permits investigators and DCC staff to easily determine how many patients might be available for future network projects. For example, the NICHD-funded CPCCRN database includes 126,919 PICU admissions for 91,526 different children, and the records are preprocessed so that queries provide near-instantaneous responsiveness.

The user is given a list of dimensions (Figure 11a) by which they can analyze the chosen measure, which may either be individual patients or PICU admissions. By selecting the site and year, the numbers of patients available each year in each site is instantly displayed (Figure 11b). Replacing the site dimension with the Major Diagnostic Category (MDC) and restricting to the top eight categories yields numbers of patients within each MDC by year (Figure 11c). This data warehouse is used extensively by network investigators and DCC staff, and has been extremely useful for providing initial feasibility data for network study concepts.

7.3.3 Clinical Trial Software: OpenClinica

The DCC uses an open source clinical trial data management system called OpenClinica. The backend database is PostgreSQL, an open source, high performance database. OpenClinica allows DCC staff to construct studies conceptually, and it then automatically generates the Internet Web pages (an example is shown in Figure 12). It supports sophisticated skip patterns, field validation, alerts, and range checks. It also maintains an audit of all changes in data fields. Reports can be generated at the DCC, and there is an automated extraction function that produces SAS files with formatting statements, using

Figure 12: Sample Web page of clinical trial software.

CDISC industry standard ODM output.

OpenClinica is used as a Web-based tool for data entry, but the trial databases are maintained in Microsoft SQL Server, as described earlier. We have developed software that automatically builds a data warehouse for all supported studies at midnight, extracting data from the PostgreSQL database used by OpenClinica, and all daily activities are based on this warehouse. This eliminates problems with on-going data entry and potentially confusing changes in the database if investigators receive data at different times during the day. All reports from the database include an indication of the database snapshot from which the reports are generated. Data that are collected by direct importation from other databases, such as is proposed in Specific Aim Three, are directly placed in SQL Server, skipping OpenClinica. This approach is also used for importing data from other laboratories, such as biomarker measurements, to avoid using Web based data entry that requires human interaction.

While OpenClinica is open source, it is also backed by a commercial company (OpenClinica, LLC) and the DCC purchases support from the company to assure that our server instance meets regulatory validation and receives continuous updates.

7.3.4 Web Server Software

The DCC currently hosts Internet Web sites for CPCCRN (Figure 13 on the facing page), PECARN, THAPCA, the Intermountain Injury Control Research Center (IICRC), the National EMSC Data Analysis Resource Center (NEDARC), the Utah State Trauma Registry, and the National EMS Information System Technical Assistance Center. We host these sites with Microsoft Internet Information Services (IIS) or the open source Apache

software. Confidential information is not included on these sites because all internal network study communication is done in eRoomTM. The purpose of the public Web site is to inform the public and non-network investigators about the network, providing contact information for potential collaborators.

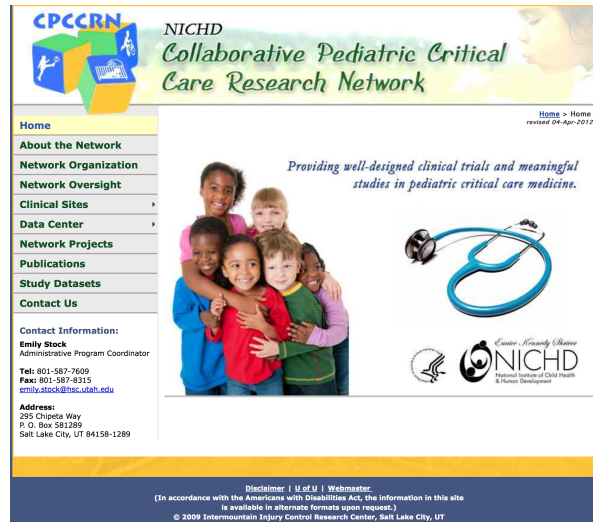


Figure 13: Public Website for CPCCRN

7.3.5 IICRC Query Management System

While the electronic data capture system (OpenClinica) has data field validation, sophisticated validation of data between different forms requires processing after data are submitted to our site. We have written a Java-based application called the IICRC Query Management System, and use it to manage all queries for studies supported by our staff. For each study, the clinical data manager determines the business rules for each data element, and SQL queries are written to enforce each rule. The system executes during the night, identifies all new data discrepancies, and creates a single email to each site research coordinator that contains all the new discrepancies. Discrepancies are not repeated in email notification for seven days, a feature appreciated by research coordinators. Most importantly, if the data discrepancy is corrected by the site research coordinator, the system automatically resolves the query without requiring DCC staff intervention. If the research coordinator needs to communicate with the clinical data manager and request manual resolution, this is also done through the system, so a complete audit trail is available for all data element changes and query resolutions.

Supported investigators, research coordinators, and supervisory staff can view real time data quality reports by specific clinical sites or individual query rules, by date of occurrence and resolution, or by aging of queries (Figure 14 on the next page). This software provides us a powerful management tool for monitoring data quality. Finally,

Site ID	Site Name	Aging(days) of Resolved Queries				Total Resolved
		within 7	8 - 14	15 - 21	22 or more	
CHLA	Childrens Hospital Los Angeles	1433	405	269	618	2757
CHOM	Childrens Hospital of Michigan	1750	228	68	328	2420
CHOP	Childrens Hospital of Philadelphia	1875	385	205	701	3181
CNMC	Childrens National Medical Center	2197	261	27	297	2841
UCLA	Mattel Childrens Hospital at UCLA	498	211	95	415	1227
PHNX	Phoenix Childrens Hospital	1655	178	51	329	2233
MICH	University of Michigan Medical Center	1840	307	180	652	2996
UPMC	University of Pittsburgh Medical Center	715	273	143	877	2011
All Site Total		11963	2248	1038	4217	19666

Figure 14: Query System Aging Report of Resolved Queries

the system maintains an audit trail of all queries, query communications, and query resolution.

7.3.6 Statistical Software

We use SASTM Version 9.1 for most analyses, but also use R and S-PlusTM for selected types of analysis. SUDAANTM is available for longitudinal nested studies. EASTTM is used for the design and simulation of studies incorporating sequential monitoring designs. The software allows the design of superiority, futility only, and non-inferiority trials, for any type of endpoint, with appropriate adjustment of Type I error and power. Simulations allow comparison of statistical power and other characteristics of competing designs; the interim-monitoring module allows calculation of exact inference at any interim analysis, and facilitates conditional power calculations. We have other specialized statistical software, including StatXactTM (exact statistical methods based on permutation procedures, for small sample categorical and non-parametric data), and LogXactTM (exact small-sample logistic regression).

7.3.7 Webconference Software

The DCC uses Adobe ConnectTM software for web conferences. This software enables us have concept presentations during investigator teleconferences, and facilitates training of research coordinators between Steering Committee physical meetings. We can also record the content of the meetings for later review.

7.3.8 On-Line Training Software

The DCC uses Moodle, an open source free software product to support on-line learning; this software is installed in over 85,000 institutions and has been used by over 65 million users. Moodle includes the ability to provide complete audio recorded presentations. Figure 15a on the facing page shows a list of the four modules dealing with workflow

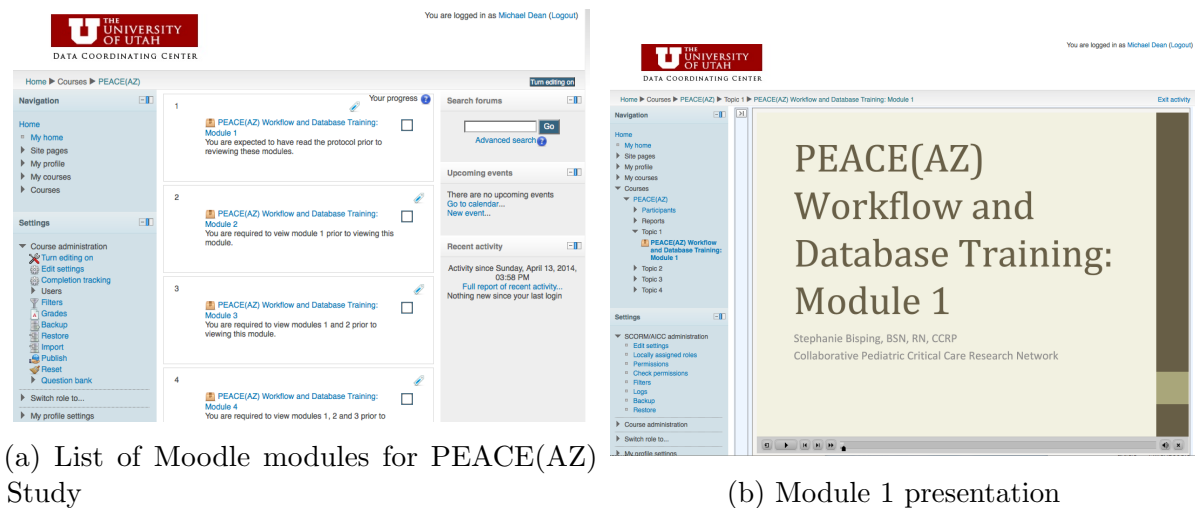


Figure 15: On-line study training with Moodle system.

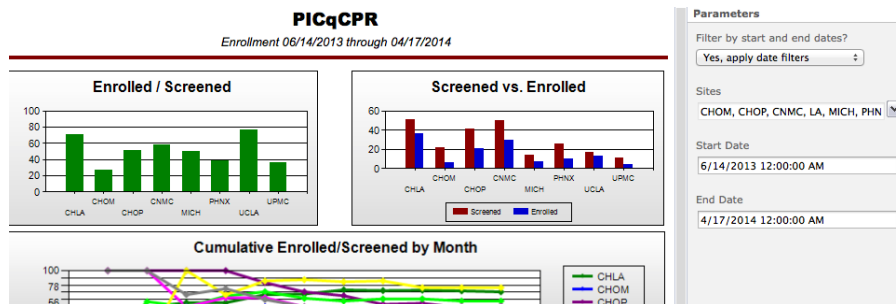
in the PEACE(AZ) study being conducted by CPCCRN; the first module is shown in Figure 15b. The user can start and stop the presentation at will, and at the end of the presentation, a quiz is provided. The software tracks individual users, and certificates are issued when a user has completed all the lessons and passed all the quizzes. We believe that training at Steering Committee meetings is very important, but the on-line training capability is important because of inevitable turnover of research coordinator staff at participating DECAAF-II sites.

7.3.9 Real Time Reporting Software

The DCC uses SharePoint, a secure information sharing platform that enables organizations to manage information and collaboration effectively. The DCC uses SharePoint as the central application that consolidates study data and translates that data into information. Every DECAAF-II investigator, and research coordinator will have accounts for real-time access to network or study level performance metric reports, study demographics, enrollment and data quality reports. In CPCCRN, these are organized through the main site (Figure 16 on the following page), and if the user selects PICqCPR from the list on the left side of the Figure, study accrual information from this study is provided (Figure 17 on the next page).

The default setting for all reports displays all sites and includes the entire duration of each study. Transparency about site performance enables the sharing of best practices from high performing sites, and the opportunity for improvement for sites performing at a lower level. An important feature of these reports is the ability for users to customize the date range and sites included in the report (see right side of Figure 16 on the following page); this allows a site to compare its performance at different time points in a study.

Figure 16: Main reporting page



(a) Graphical display of study enrollment.

Site	IRB Approval	Screened ¹	Enrolled ²	Enrolled / Screened	PICqCPR Event Location ³		
					PICU	CICU	Unknown
CHLA	06/20/2013	51	36	70%	14	22	0
UCLA	06/12/2013	17	13	76%	5	8	0
CHOM	05/10/2013	22	6	27%	6	0	0
CHOP	06/04/2013	41	21	51%	6	15	0
CNMC	06/21/2013	50	29	57%	7	22	0
MICH	05/10/2013	14	7	50%	4	3	0
PHNX	07/08/2013	26	10	38%	5	5	0
UPMC	05/20/2013	11	4	36%	4	4	0
		243	130	53%	51	79	0

1 Screened is defined as the CPR event meeting all inclusion criteria.
 2 Enrolled is defined as meeting all inclusion and exclusion criteria.
 3 PICqCPR Event Location represents enrolled subjects only.
 * Data Last Updated 4/17/2014

(b) Tabular summary of study enrollment.

Figure 17: Accrual report for PICqCPR study.

CPCCRN Study Enrollment Report							
Enrollment 06/12/2007 through 04/17/2014							
Study Site	Study	IRB Approval	Screened	Eligible	Approached	Enrolled ¹	Enrolled / Eligible
CHLA	Critical Pertussis	11/16/2007	NA	11	11	11	100%
	THAPCA	03/26/2009	180	67	64	49	73%
	TOPICCII	06/24/2011	NA	2116	NA	1130	53%
	BATE	11/27/2012	51	NA	NA	50	98%
	PICqCPR	06/20/2013	51	NA	NA	36	70%
	PEACE(AZ)	12/17/2013	NA	NA	NA	0	0%
UCLA	LAPSE	03/06/2014	0	NA	NA	0	0%
	Critical Pertussis	03/13/2008	NA	1	1	1	100%
	THAPCA	04/02/2009	70	24	19	13	54%
	TOPICCII	06/29/2011	NA	830	NA	433	52%
	BATE	12/06/2012	21	NA	NA	21	100%
	PICqCPR	06/12/2013	17	NA	NA	13	76%
	PEACE(AZ)	01/06/2014	NA	NA	NA	0	0%

Parameters

Filter by start and end dates?
 Yes, apply date filters

Sites
 CHOM, CHOP, CNMC, LA, MICH, PHN

Start Date
 6/12/2007 12:00:00 AM

End Date
 4/17/2014 12:00:00 AM

Figure 18: Example site performance summary report.

We also provide summary reports to easily assess overall site performance (Figure 18). This report may also be customized by site and date range, enabling DECAAF-II trial staff to identify performance improvement at sites during the studies.

8 Protection of Human Subjects

8.1 Institutional Review Board (IRB) Approval

The Data Coordinating Center (DCC) and each Clinical Center must obtain approval from their respective IRB or Research Ethics Board (REB), or equivalent prior to participating in the study. The Data Coordinating Center will track IRB approval status at all participating Clinical Centers. The DCC will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

8.2 Informed Consent

Potentially eligible subjects will be approached to discuss participation on the study. Research staff will describe the objectives and procedures associated with the study, the risks, and potential foreseeable risks associated with the research. Research staff at Clinical Centers will obtain the subject's informed consent prior to initiation of study activities. Documentation of consent will be the responsibility of the Clinical Center.

8.3 Potential Risks

Catheter-based atrial fibrillation (AF) ablation is an accepted treatment for atrial fibrillation and is widely used as a treatment for patients with persistent or paroxysmal AF. Subjects in this trial will receive standard-of-care PVI ablation in both treatment arms.

The general risks and benefits of catheter-based ablation for AF, e.g. cardiac perforation, pulmonary vein stenosis, stroke, death, and bleeding or pain at the insertion site, are outlined in the standard medical procedure consent forms at respective Clinical Centers.

There are potential risks related to the fibrosis-guided ablation procedures. Due to the longer time under anesthesia, more areas being ablated and longer total procedure time, subjects in the fibrosis-guided ablation group are at greater potential risk for scarring, injury to peri-esophageal vagal nerves, esophageal injury, cardiac perforation, and atrial esophageal fistulas.

Because there are extra potential risks associated with the procedures for the fibrosis-guided ablation, some subjects will be randomized into a group with more overall risk. Agreeing to participate means that subjects are willing to accept the possibility of being exposed to these added risks. This risk is offset in part by the potential benefit from fibrosis-guided ablation, which may provide better clinical outcomes.

Women who are pregnant are excluded from the trial. Premenopausal females will be given a urine pregnancy test before ablation. If a subject becomes pregnant while taking part in the study, the participant will be instructed to immediately notify the research doctor. This situation, though possible, is unlikely since the majority of subjects will be older in age. A pregnancy test is standard of care for pre-ablation procedures and will not be paid for by the study.

The small amount of blood drawn for the study will pose minimal risk e.g. bleeding, pain, or hematoma at the puncture site.

There is minimal risk of accidental disclosure of subject identity and health information.

8.4 Protections Against Potential Risks

The daily ECG transmissions will potentially detect treatment failure faster than routine follow up and will provide additional safety over and above standard of care. The ablation protocols for both study arms are described in this protocol, but these approaches allow for clinical judgment during ablation procedures. Ablation procedures will be guided by the DE-MRI image in the treatment arm, which may result in additional ablation, but clinicians must always exercise judgment in ablation procedures for each subject. Adverse events will be tracked during the study and serious adverse events will be promptly reported to the Data Coordinating Center.

Study information will be kept in a secured manner and the database will be password protected. Loss of confidentiality is mitigated by the use of the Data Coordinating Center which has a highly secure IT infrastructure. Data security is described in Section [7.2.2 on page 33](#).

8.5 Potential Benefits for Subjects

Subjects receiving fibrosis-guided ablation targeting atrial fibrosis may stay in a normal heart rhythm and may have fewer AA recurrences than those who receive conventional pulmonary vein isolation (PVI) ablation. There is potential for direct benefit for the participants in this study who receive the DE-MRI guided catheter-based ablation.

The study also makes use of new technologies that allow closer and more frequent monitoring of patients' heart rhythm. Subjects in this study, regardless of arm assignment, will receive the mobile heart monitoring device (*ECG Check*) to complete regular monitoring of their heart rhythm after the ablation procedure. This may allow for earlier detection of AA recurrence and may also reveal other arrhythmias of clinical significance. Thus, subjects may experience an enhancement in quality and frequency of monitoring using the ECG device. ECG output will be reviewed regularly by a trained nurse (or other trained individual), and a specified individual at each Clinical Center will be made aware of atrial arrhythmia recurrence or other rhythms that may be considered clinically significant. The Data Coordinating Center will receive regular ECG data transmissions and will automatically notify sites of AA recurrence so that clinicians may contact subjects if they choose. Subjects will be instructed to contact their local physician or local emergency services if they experience any symptoms, as ECGs will not be read in real time.

The second MRI scan will provide information about early post-ablation scar formation and the presence and degree of pulmonary vein stenosis. This information may be clinically beneficial to patients in both arms of the study. For example, it has been shown that post-ablation scarring correlates with procedure outcomes and AF recurrence.^{19, 20} In addition, any progression of PV stenosis confirmed by an MRI scan 3 months post-ablation may be implicated in the future development of severe stenosis.²¹

8.6 Potential Benefits for Future Patients

Future patients with atrial fibrillation will benefit from the study if the results determine that one treatment regimen is superior to others in decreasing the recurrence of atrial fibrillation.

8.7 Withdrawal from Study

A subject may withdraw from the DECAAF-II study at any time. If a subject withdraws permission to continue in the study, all study interventions will be discontinued, but the medical course of the patient will continue to be followed for adverse events until the patient has reached the administrative endpoint of the study.

9 Data and Safety Monitoring Plan

9.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB). The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as described on page 31. The purpose of the DSMB is to advise the sponsors and Principal Investigator(s) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual Clinical Center, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy.

The DCC will send reports relating to these topics to DSMB members prior to each DSMB meeting. Interim analyses are anticipated after approximately 1/3 and after approximately 2/3 of the projected total number of events have occurred. The DCC will staff the DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by the DSMB Chairperson. These closed minutes will not be available outside the DSMB prior to the end of the study. The DSMB Chairperson will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. The summary will be provided to the DCC, and the DCC will send the summary to all Clinical Center investigators for submission to their respective Institutional Review Boards/Research Ethics Board(s).

9.2 Adverse Event Reporting

Assuring patient safety is an essential component of this protocol. Each participating Clinical Center investigator has primary responsibility for the safety of the individual subjects under his or her care. Clinical visits will occur at months 3 and 12 months. Site staff will also call the subject at 6 Month. For subjects whose follow-up period extends to 18 months site staff will conduct a chart review and call the subject to identify any additional adverse events. Clinical investigators may schedule additional clinic visits according to their standard of care or as needed for clinical reasons. At regular study visits, and at any scheduled or unscheduled visits in the first 30 days, the Clinical Center staff will record all new or worsening symptoms or events as reported by the patient. After the 30 days until the end of study assessment we will collect cardiovascular, cerebrovascular, and gastrointestinal adverse events and serious adverse events. The 2012 HRS consensus statement² will be used for guidance in capturing these adverse events.

All adverse events meeting these definitions occurring after study randomization through final follow up will be recorded and entered into the electronic data entry system provided by the DCC. In accordance with local IRB/REB requirements, the Clinical

Center investigator may be required to report such events to the IRB/REB in addition to notifying the DCC.

9.2.1 Definitions, Relatedness, Severity and Expectedness

Definition: An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. The Clinical Center investigators will evaluate adverse events. Adverse events will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established. Arrhythmias will not require reporting as adverse events because patients will be transmitting daily ECGs using the mobile device, and these will be regularly reviewed and interpreted by the central monitoring team. ECG findings will also be reported to the DCC and recorded in the study database. In addition, the *ECG Check* phone application will pose a series of short, simple questions to the subjects with the goal of identifying symptoms and hospitalizations experienced by the patient. These questions will appear on the subject's phone regularly (e.g. every other week).

Subjects will indicate the presence of specific symptoms, and these data will be sent to the Clinical Center, for research purposes, and will also be transferred to the database at the DCC. If subject provides a positive answer to the symptom question or the hospitalization question the site will be informed for research purposes. Clinical site investigators may choose to contact patients based on symptom reports but these data may not be reviewed clinically or may not be reviewed in real time depending on availability of qualified staff. Symptoms or hospitalizations recorded by the subject will be part of the DSMB reporting (as outcomes).

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the following criteria. *Relatedness may not be assessed by a research coordinator, and must be assessed by an investigator.*

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and *cannot be reasonably explained* by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Seriousness: The severity of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with atrial fibrillation, ablation procedures, other underlying medical conditions of the subject, is directly related to study outcome, or is otherwise mentioned in the protocol, informed consent, or other study documents.

Expected complications of atrial fibrillation or standard catheter ablation procedures include development of atrial-esophageal fistula or injury, pulmonary vein stenosis, cardiac tamponade, cardiac perforation, esophageal injury, embolic events, stroke, phrenic nerve injury, mitral valve trauma, air embolism, acute coronary artery occlusion, and death. Catheter entry site complications include swelling, bleeding, pain, hematoma at catheter entry site(s).

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

9.2.2 Time Period for Adverse Events

For purposes of this study, adverse events will be recorded for the period following randomization through the final follow up visit.

9.2.3 Data Collection Procedures for Adverse Events

In the first 30 days after randomization, all adverse events (including serious adverse events), whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. In the time frame 30 -day post-ablation until end of study cardiovascular, cerebrovascular and gastrointestinal adverse events whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the site investigator will assess the severity and relationship to the study. Laboratory values that are abnormal at the time of randomization and that do not worsen will not be recorded as adverse events.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center because this requires specific training.

9.2.4 Unanticipated Problems (UP)

Unanticipated problems (UP) are deemed as incidents, experiences, or outcomes that are unexpected, related to participation in the DECAAF II study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The Clinical Center investigator will report unanticipated problems to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the DSMB in an expedited manner (within 24 hours). In accordance with local IRB requirements, the Clinical Center investigator may be required to report such unanticipated problems to the IRB in addition to notifying the DCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and the DSMB cannot be reached expeditiously, the DCC will notify the study investigator (Dr. Marrouche) and all investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the DSMB.

9.2.5 Monitoring Serious Adverse Events

The Principal Investigator of the Data Coordinating Center (Dr. Dean) will act as the medical monitor for this study. If Dr. Dean is unavailable, a qualified physician will be designated to fulfill this function. Site investigators and/or research coordinators will report serious adverse events to the Data Coordinating Center within 24 hours. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign each SAE report after review. All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by DSMB members.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or the DSMB chairperson cannot be reached expeditiously, the DCC will notify the study investigator (Dr. Marrouche) and all Clinical Center investigators to cease enrollment in the trial. Resumption of enrollment will not occur without the approval of the DSMB.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

After notification of the DSMB chairperson of serious, unexpected, and study-related adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Marrouche) and all clinical investigators, who will be instructed to report this to their local IRB or ethics boards.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

9.2.6 Follow-up of Serious, Unexpected and Related Adverse Events

Serious adverse events, that are unresolved at the time of the patient's termination from the study, will be followed by the Clinical Center investigators until the events are resolved, the subject is lost to follow up, or the adverse event is otherwise explained or

has stabilized.

10 Study Training and Monitoring

10.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics including applicable regulations and good clinical practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The DCC, in collaboration with the study investigator (Dr. Marrouche), will be the main contact for study questions.

10.2 Study Monitoring

The investigator recognizes the importance of ensuring data of excellent quality, and site monitoring is critical to this process. We will utilize site monitoring as a part of a risk-based monitoring plan to ensure excellent quality data in the proposed study. Site monitors will monitor enrolling centers during the trial to assess protocol and regulatory compliance as well as data quality. The timing, frequency and method of interim monitoring will be outlined in a separate site monitoring plan. Select sites may be monitored remotely. Remote access monitoring, e.g., gaining access to electronic health records, and consent forms, and regulatory documents may supplement or in some circumstances replace on-site visits for very low enrolling sites. Participating Clinical Center staff must make medical records, regulatory and study documents available to the monitor or DCC staff as requested to assure quality and study protocol compliance. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

10.2.1 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol, will be completed which outlines specific criteria for monitoring of the trial. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review, and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all subjects within a site; key data or all data), the schedule of when these activities are to take

place, how they are reported, and a time frame to resolve any issues found. Remote site monitoring data elements and schedule will be determined by the DCC.

10.2.2 Clinical Site Monitoring

Site monitoring visits will be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on risk assessment, budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close out visit. The site initiation may take place as group training made up of site investigators and research assistants.

10.2.3 Remote Monitoring

The DCC will supplement on-site monitoring with remote monitoring activities. Remote monitoring involves review of the data entered by staff coordinators or physicians and source documents to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record to the DCC staff, who review those materials against the data recorded in the electronic data capture system. Some sites may elect to provide remote access to documents for quality review.

11 Regulatory Issues

11.1 Food and Drug Administration

In this trial, 3 different U.S. Food and Drug Administration (FDA) approved devices will be utilized. All three devices also have a CE- mark and approved in Europe. The first is a hand-held ECG application that transmits the ECG. This device has been approved for the transmittal of ECG information. The second is a software application for viewing and post-processing of cardiovascular MRIs to obtain left atrial enhancement quantification and visualization on a 3D model, which has been previously approved for this indication. Finally, ablation catheters that are used for atrial fibrillation treatment are being used in their approved manner. Although this trial will be the first to use all 3 devices together, this use does not necessitate a new IDE as this composite utilization falls within current approvals for each device for their approved indications.

11.2 Health Insurance Portability and Accountability Act

The abstracted data will include limited identifiers as defined by the Health Insurance Portability and Accountability Act, such as dates of birth and service. Abstracted data

will be retained and archived at the Data Coordinating Center in accordance with record retention requires of the Food and Drug Administration and the NIH. Contact information will not be provided to the Data Coordinating Center (it will be provided directly to the central follow up research staff). For data analysis outside the Data Coordinating Center (e.g., when a public access database is made available), the Data Coordinating Center will create a completely de-identified analytical database for use by the study investigators, and for final archiving. All U.S. study sites have been or will be offered Business Associate Agreements with the University of Utah. Copies of signed Business Associate Agreements are maintained at the Data Coordinating Center.

11.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

11.4 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

11.5 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the the Food and Drug Administration, and the Institutional Review Board (IRB) for each study site.

11.6 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

12 Data Sharing Plan

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be

recorded in a manner that will make it impossible to deduce or impute the specific identify of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies to be determined by the DECAAF-II Investigators and sponsors, the releasable database will be provided to users in electronic form. The DCC is able to produce a relational database export, or use SAS or SPSS data sets.

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DECAF II PROTOCOL FINAL VERSION



**Efficacy of DE-MRI-Guided Fibrosis Ablation vs.
Conventional Catheter Ablation of Atrial Fibrillation
(DECAAF II)**

University of Tulane

Protocol Version 2.03
Version Date: July 9, 2019
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This protocol has been authored by Dr. Nassir F. Marrouche at the University of Utah.

This document was prepared by the Data Coordinating Center (DCC) located at the University of Utah School of Medicine, Salt Lake City, Utah. The document was written and typeset using $\text{\LaTeX} 2_{\epsilon}$.

PROTOCOL TITLE:

Efficacy of DE-MRI-Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation

Short Title: DECAAF II

Lead Investigator and Author:

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University of Tulane

Protocol Version: 2.03

Version Date: July 9, 2019

I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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1 Background and Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of people in the US and around the world. Treating AF continues to be a challenge. Over the last 15 years, catheter based AF ablation procedure has been widely adopted. Approximately 50% of patients treated with catheter ablation present with a persistent type of the arrhythmia. Unfortunately, ablation results in this population have been dismal, not only because of low success rates in suppressing arrhythmias, but also from a healthcare cost point of view. In fact, the long-term success of such a procedure has been reported to be as low as 20%, and patients may need more than two ablation procedures to achieve temporary arrhythmia suppression. The cost of AF ablation among Medicare patients followed for a year after ablation was found to be US\$16,049 \pm \$12,536 if ablation was successful versus US\$19,997 \pm \$13,958 for failed ablation.² A major issue contributing to the low success of catheter ablation is the lack of a protocol to appropriately select patients that would respond to this treatment. Currently, cardiologists base their decision to ablate persistent AF on various comorbidities, a concept that has not been proven successful. With the introduction of AF ablation as a first line therapy option in the AHA/ACC/HRS 2012 guidelines,³ a better and more accurate selection protocol is urgently needed.

There is a strong association between AF and atrial tissue fibrosis. Recently, a novel DE-MRI (Delayed-Enhancement MRI) based imaging modality has been demonstrated to reveal the degree of fibrotic atrial tissue in patients suffering from AF.⁴⁻⁶ When applied in various studies, including a multi-center study, extent of fibrotic atrial changes was shown to be the strongest independent predictor of a successful treatment in patients undergoing ablation of AF. Moreover, in the multi-center observational study DE-MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF), the strongest independent predictor of successful outcome was the surface area of fibrosis covered by ablation lesions. In fact, the number of encircled pulmonary veins, the most common adopted approach to ablate AF today, did not predict catheter ablation success.¹

The use of non-invasive ambulatory electrocardiography (ECG) devices including 24-48 hour Holter monitors and 30-day cardiac event monitors have been widely used for the detection of cardiac rhythm abnormalities. The duration of time for rhythm evaluation is key to detect arrhythmias and conduction abnormalities, as number of arrhythmia diagnoses increases with increasing duration of monitoring. The longer duration of monitoring occurs at the expense of patient comfort and patient compliance. Previous FDA-approved devices for standard of care monitoring are limited in the duration of monitoring. At many institutions, it is standard of care to wear a 60-day cardiac event monitor for the detection and evaluation of cardiac arrhythmias in the post-ablation blanking period.

The percentage of asymptomatic recurrences of AF drastically increases after ablation.⁷ Thus, post-procedure devices are necessary for close monitoring and detection of asymptomatic AF in ablation patients. Compliance with the current cardiac event

monitors may be low for many reasons. Electrode intolerance due to skin rashes, irritation and/or breakdown, and the unwillingness for continuous devices to be worn are some known areas of non-compliance.

In this study, a higher level of monitoring will be provided with use of new wireless ECG technologies,⁸⁻¹⁰ specifically, the FDA approved *ECG Check* mobile heart monitor designed by Cardiac DesignsTM. This mobile heart monitor will enable patients to record their heart rhythm anytime and anywhere. The device will automatically analyze the ECG for symptomatic or asymptomatic arrhythmias for the duration of their life as long as it is compatible with their current “smart phone”. This is a patient-owned monitor.

The *ECG Check* is the first FDA-approved over-the-counter ECG monitor that is currently compatible with iPhone[®] 4S and newer, and approved Android mobile phones. *ECG Check* has also been approved in Europe and has a CE-Mark. This will allow patients to record, store, transfer and analyze single-channel ECG wirelessly through the *ECG Check* app (available for free in the iTunes App Store) and the *ECG Check* Web Center. The information will be uploaded to a protected server through Cardiac DesignsTM.

This proposal is aiming at modifying and improving persistent AF management guidelines by evaluating targeting DE-MRI detected atrial fibrosis during AF ablation and its related effect on procedural outcome.

2 Study Objectives and Endpoint Definition

Primary Objective. To examine the efficacy of targeting atrial fibrosis tissue during an ablation procedure in treating persistent AF.

Results from the DECAAF study show that one of the most important predictors of ablation outcome was the degree of ablation of the fibrotic tissue; the more fibrotic tissue that was overlapped with scar during ablation, the better the outcome. These results were the impetus for the primary objective of DECAAF II. Patients will be randomized to receive conventional pulmonary vein isolation (PVI) ablation or PVI + fibrosis-guided ablation. We will follow patients longitudinally to assess recurrence of persistent atrial arrhythmias (AA) (atrial fibrillation, atrial flutter or atrial tachycardia as defined by recent AHA/ACC/HRS guidelines³). We hypothesize that patients receiving fibrosis-guided ablation in addition to conventional PVI ablation will have fewer AA recurrences than those who receive PVI ablation alone.

We will also examine the efficacy of the fibrosis-guided ablation intervention on a number of secondary or exploratory outcomes including the individual components of the primary endpoint (atrial fibrillation, atrial flutter and atrial tachycardia), symptomatic

atrial arrhythmia, cardiovascular (CV)-related hospitalization, CV-related mortality, quality of life measurements (University of Toronto Atrial Fibrillation Severity Scale (AFSS), and AF burden.

The safety of the two interventions will be evaluated by peri-procedural complications including stroke, pulmonary venous stenosis, bleeding, esophageal injury, cardiac perforation, heart failure, and death.

Our study patients will be followed using the FDA-approved mobile *ECG Check* application. Clinical Center personnel will instruct consented subjects to record ECG data from the *ECG Check* application daily on a smart phone. ECG data will be automatically sent to the central ECG review team. We anticipate that daily ECG follow-up will provide a better-defined endpoint than less frequent follow up assessments as used in previous AF trials.

Definition of Primary Endpoint. The primary endpoint of the study is the recurrence of atrial arrhythmia post-ablation.

The primary endpoint is defined as the first occurrence of atrial fibrillation, atrial flutter, or atrial tachycardia demonstrated after the 90-day post-ablation blanking period by either:

- a) The occurrence of a single positive reading obtained on a 12-lead ECG or Holter monitor or other continuous heart monitoring device.
- b) Two positive readings from the ECG Check device obtained at least 6 hours but no more than 7 days of each other.

It is difficult to anticipate whether the subject population will have technical difficulty or accessibility issues using the smart phone on a daily basis. Hence, if the patient is unable to continue to use the *ECG Check* mobile device, the patient will be monitored for atrial arrhythmia recurrence using 12-lead ECGs, Holter or other continuous monitoring devices as part of standard of care for the remainder of the patients follow-up period. A 12-lead ECG is required at the end of study assessment period for patients without an ECG assessment within 3 months of the end of follow-up. If a subject undergoes a second ablation procedure during the study period (after the 90-day blanking period) but does not have a documented atrial arrhythmia by the methods described previously, the ablation will also constitute a study endpoint. Ablations occurring within the 90 day blanking period will not be counted as an outcome.

3 Study Design

DECAAF II is a prospective, randomized, multi-center trial of patients with persistent AF and presence of atrial fibrosis. After consenting to participate in the study, the subject will undergo a DE-MRI scan to assess for extent of atrial fibrosis. After verifying adequate quality of the DE-MRI study, subjects will be randomized to one of two study groups to receive conventional PVI ablation (Group 1) or PVI + fibrosis-guided ablation (Group 2), as summarized in Figure 1. In Group 1, PVI ablation will be performed as recommended by the HRS consensus statement³ and physicians will be blinded to the pre-ablation MRI fibrosis results. A blank 3D model will be provided to the provider. In Group 2, physicians will receive the DE-MRI scan prior to the ablation procedure, will complete conventional PV isolation, and will also target left atrial fibrosis detected by MRI.

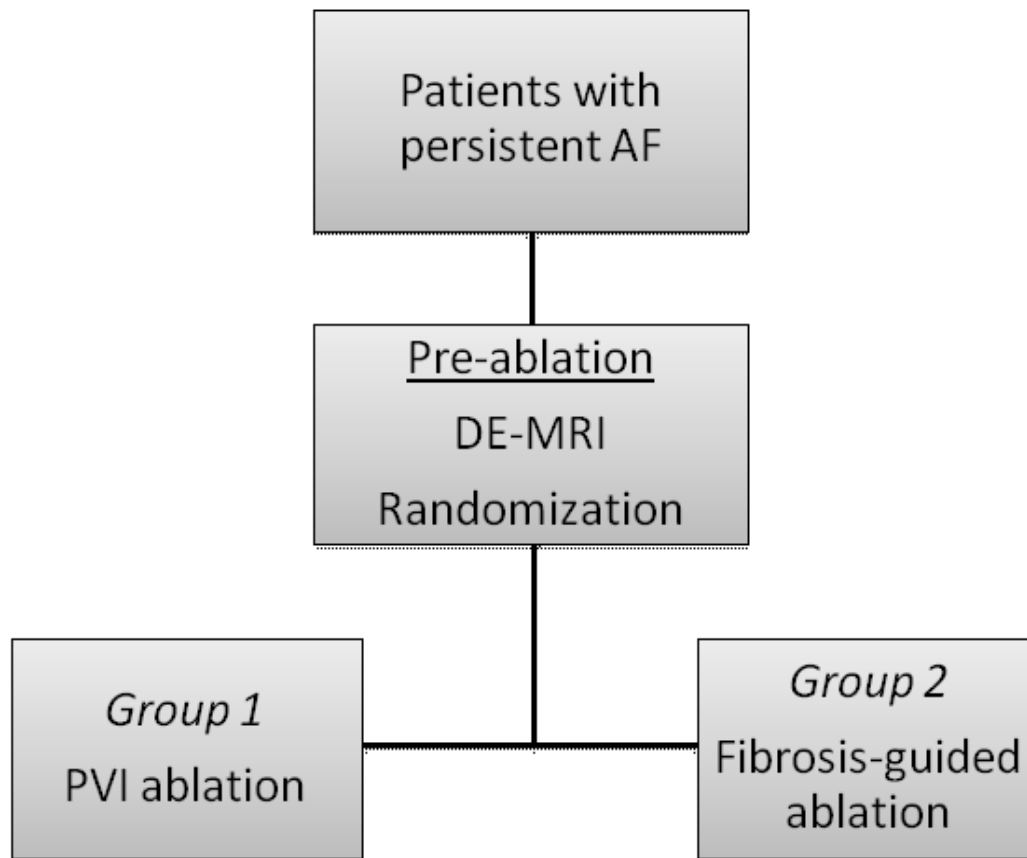


Figure 1: DECAAF-II Study Summary.

Patients randomized prior to November 10, 2017 will be followed for 18 months following the ablation procedure. Patients randomized between November 11, 2017 and May 10, 2018 will be followed until May 10, 2019, providing a follow-up period between 12 and 18 months depending on the patient's randomization date. Patients randomized

after May 10, 2018 will be followed for 12 months following the ablation procedure. The trial will be analyzed as an intention-to-treat trial.

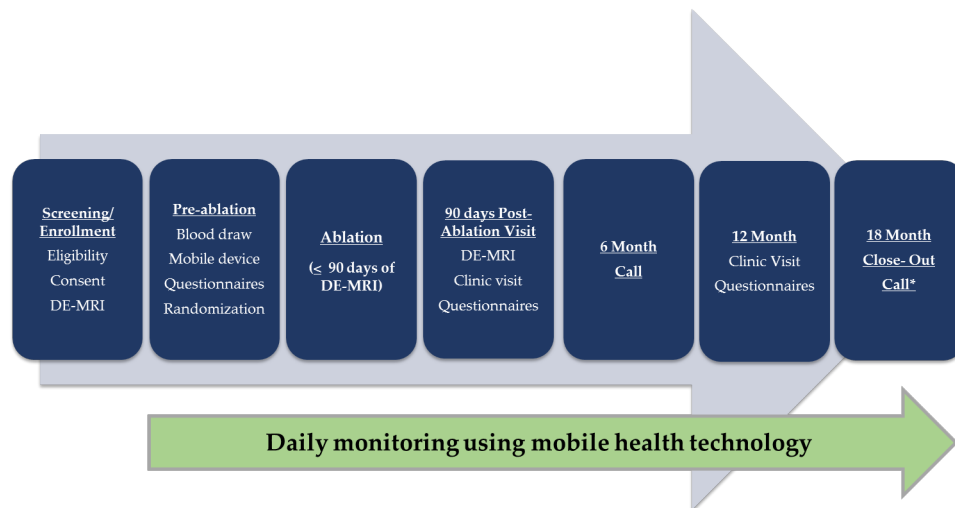


Figure 2: DECAAF-II Workflow

*Patients randomized after November 11, 2017 will have a final close out call between 12 and 18 months after randomization.

This trial has an enrollment target of 900 randomized patients. This is based on the assumption that 40% of patients will reach the primary AA recurrence outcome.

Project Enrollment and Follow-up Timeline. The duration of this study is estimated at 5 years.

This will include 9 months allotted for developing materials, IRB approvals, startup activities, and rolling patient enrollment, approximately 12 months for follow-up after the last patient is randomized, and 6 months for close-out activities and manuscript preparation. Our success with DECAAF and the basic inclusion criteria highlight the feasibility of this project to be completed within 5 years. In addition, many of these Clinical Centers participated in DECAAFI and presented successful recruitment. A flowchart depicting patient flow through the study is presented in Figure 2.

4 Study Procedures

4.1 Site Selection

All DECAAF II recruiting sites have been or will be pre-screened for eligibility. Sites must have recruitment potential (> 300 persistent AF ablation cases per year) and the proper infrastructure for fibrosis imaging (ability to perform delayed enhancement MRI and Magnetic Resonance Angiography (MRA)). Prior to enrolling subjects, sites may submit sample pre-trial DE-MRI and Magnetic Resonance Angiography (MRA) scans for review and feedback by the imaging team at the University of Utah. Pre-trial scans will be used to identify typical problems during MRI acquisition and provide additional training. Additional scans may be requested if the research site has not demonstrated aptitude for adherence to MRI protocol (e.g. timing between contrast injection and late enhancement, position of data acquisition during cardiac cycle, duration of data acquisition window, submission of all required image sets, etc.) In addition to the pre-screening and pre-trial process, training materials giving detailed descriptions of MRI acquisition and image submission will be developed and provided to each site. Training sessions will be organized for participating sites.

4.2 Participant Eligibility

Inclusion criteria are:

1. Patients with persistent AF defined as 7 days or more of AF as evidenced by rhythm strips or written documentation; AND
2. Undergoing first AF ablation as per recent HRS consensus document³ ; AND
3. Age \geq 18 years.

Patients are not eligible for DECAAF-II if they have any of the following exclusion criteria:

1. Previous left atrial ablation or any type of valvular surgery; OR
2. Contraindication for DE-MRI with a full dose of contrast agent; OR
3. Contraindication to beta blockers, if necessary, for DE-MRI; OR
4. Women currently pregnant; OR
5. Mental or physical inability to take part in the study; OR
6. Inability to be placed in MRI due to body mass or body habitus; OR
7. Known terminally ill patients; OR
8. Subjects without daily access to a smart phone compatible with the *ECG Check* application and ability to upload ECG tracings for the entire follow up period.

4.3 Participant Recruitment and Consent

Recruitment Clinical Center staff will approach all potentially eligible patients to participate in the study. If staff decide not to approach specific patients, the reasons for not approaching the subject will be recorded.

Consent If the patient has met the eligibility criteria, the Clinical Center investigator or delegated study staff will approach the patient to explain the study and obtain informed consent from the subject to participate. The investigator or designated staff will provide an explanation of study procedures of the benefits and risks, and the costs and compensation involved with the study. Participants will be given sufficient time to read the consent form and the individual obtaining the informed consent will answer any questions posed by the participant.

4.4 Imaging Protocol

All patients will undergo a DE-MRI preferably within 30 days prior to the ablation procedure using the Marrek DE-MRI protocol (MRI sequence and Image processing software) [8-10]. If there are circumstances preventing the ablation to take place within 30 days of the DE-MRI scan, this scan can be used for the ablation procedure up to 90 days from the day it was acquired.

The purpose of the initial MRI is to quantify the degree of atrial structural remodeling or fibrosis prior to the ablation (Figure 3 on the next page). If a patient has a heart rate ≥ 90 beats per minute, they will be pre-medicated with a beta blocker prior to the MRI in order to obtain optimal images. Images will be sent to Marrek Inc., (Salt Lake City, UT) and will be reviewed for quality by trained technicians using a standard protocol. Images that do not meet quality standards will not be further processed. The site physician may opt to repeat the MRI scan and re-submit it for evaluation. If the image meets quality standards and can be processed, then Marrek will verify that the subject has some proportion of atrial fibrosis (not limited to advanced stage fibrosis). Utah Stages 1-4 (Figure 4 on page 17) will be used to classify patients based on percent fibrosis.

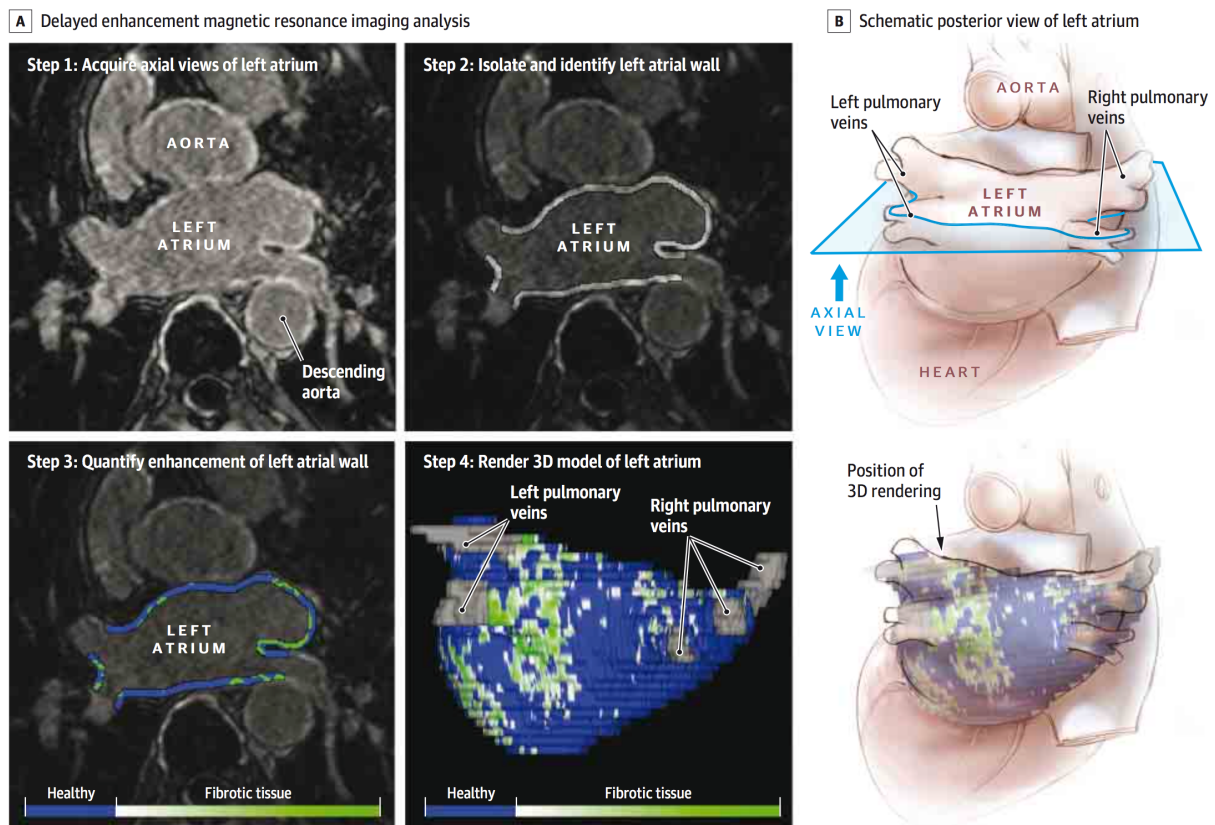


Figure 3: Process for Quantification of Left Atrial Wall Fibrosis.¹

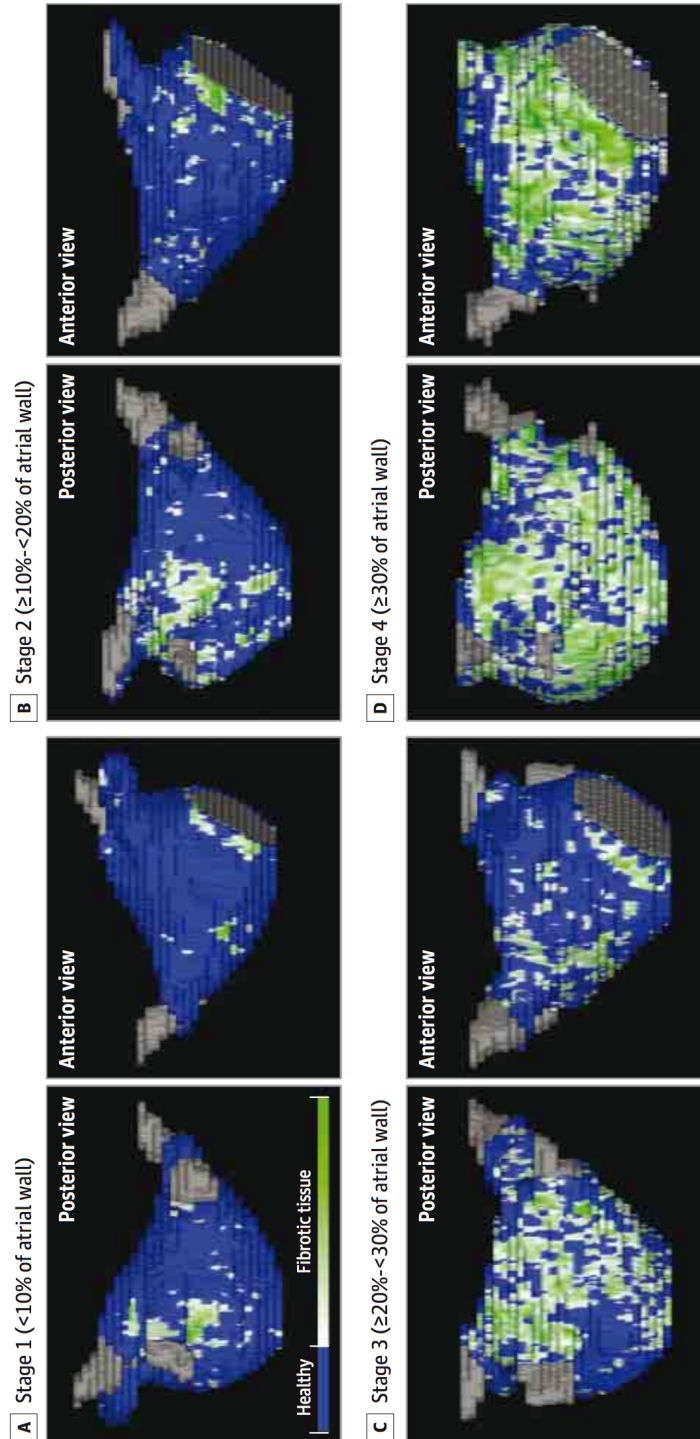


Figure 4: Four Utah Stages of Left Atrial Tissue Fibrosis.¹

Subjects for whom images are successfully evaluated and scored for fibrosis will then be randomized into the DECAAF-II study. Ablation will be carried out in accordance with the randomized arm of the study. A post-ablation DE-MRI will be obtained between 90- 180 days after the ablation to detect and quantify ablation-related scar formation. Exceptions can be granted for unforeseen circumstances. All MRI scans will be reviewed and analyzed as they arrive from each Clinical Center by Marrek, Inc. for pre- and post-ablation fibrosis and scar quantification respectively. All MRI scans will maintain identifying information to allow the Clinical Center to verify the returned scan matches the subject using their submitted identified information. MRI image processors will be blinded to arm assignment. All images will be retained at the Marrek site for storage and later analysis.

4.5 Randomization

After DE-MRI studies have been evaluated for quality and have been processed and scored for fibrosis, the DCC staff will complete randomization procedures using a web-based randomization service. Randomization will be stratified by Clinical Center and by Utah Stage¹ (with two Utah stage strata defined by Utah stages I - II, and Utah stages III - IV). For subjects who are randomized to the fibrosis-guided ablation arm (Group 2), DCC will make the processed images available to the investigator at the Clinical Center for use during the ablation procedures. Processed fibrosis images of subjects who are randomized to the PVI ablation group (Group 1) will not be made available to clinicians or site staff. All images will be retained at the Marrek site for storage and later analysis. Clinical investigators will schedule the ablation procedures to occur preferably within 30 days, but no later than 90 days after imaging has been completed.

4.6 Study Biological Samples

Blood samples will be obtained at baseline for each patient if the sites can analyze and process them. Samples will be analyzed locally for biomarkers of fibrosis and cardiovascular disease including Galectin-3, brain natriuretic peptide (BNP) and C-reactive protein (CRP), respectively. Blood samples will be processed at local sites and results will be entered into the study database. Samples will not be shipped or stored after processing.

4.7 Ablation Protocol

4.7.1 Pulmonary Vein Isolation

All pulmonary veins should be electrically isolated (Figure 5 on the next page) as described by the HRS consensus statement.³ The operator will create lesions around the PV antra. Entrance block in all pulmonary veins will be confirmed using standard techniques. Successful ablation is operationally defined as an abolishment of PV electrograms (EGMs). Assessment for the presence of exit block by pacing within the antral lesion set will be at

the discretion of the operator.

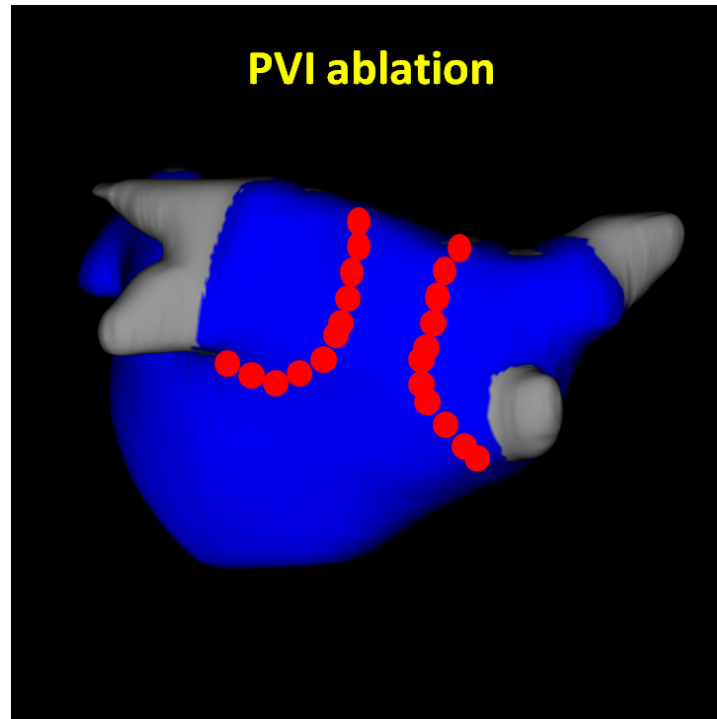


Figure 5: Isolation of the pulmonary vein.

If normal sinus rhythm cannot be restored at the end of the PVI portion of the procedure despite cardioversion in patients randomized to the conventional ablation group (Group 1), the operator may pursue further measures, such as triggering ablation, to eliminate recurrent arrhythmia if needed. The creation of a right atrial cavotricuspid isthmus line is also left at the discretion of the operator.

4.7.2 Cryoballoon Ablation

In case of cryoballoon-based antral PV isolation, it is recommended that a 28mm Arctic Front Advance balloon be used, if possible, to maximize antral ablation when isolating pulmonary veins. While the duration of energy application will be left to the discretion of the operator, we recommend the following general guidelines:

Cryoballoon temperatures below -55°C in the 28mm Arctic Front Advance Cryoballoon, or below -60°C in the 23mm Arctic Front Advance Cryoballoon require termination of energy application.

After a total of 540 seconds of cryoballoon ablation in one pulmonary vein without successful isolation, the physician is encouraged to employ a different strategy (cannulate

different vein branch, exchange the catheter for a wire) or employ a different tool (different size cryoballoon, focal cryocatheter, focal RF catheter, etc.).

4.7.3 Phrenic Nerve and Esophageal Monitoring during Cryoablation

When ablating right sided pulmonary veins, phrenic nerve pacing should be performed to ensure safe cryoablation. Additionally, we recommend ensuring the cryoballoon position is as antral as possible to avoid phrenic nerve injury. To allow pacing and monitoring the phrenic nerve, paralytics should not be administered during cryoablation. If phrenic nerve injury occurs, the operator should immediately stop ablation and force balloon deflation.

We recommend continuous esophageal temperature monitoring for cryoballoon ablation as well. As a general guideline, cryoablation should not be performed if esophageal temperatures drop below 25° C.

4.7.4 Fibrosis-Guided Ablation

For subjects randomized to the fibrosis-guided ablation group (Group 2), processed DE-MRI images will be merged with the 3D mapping system used at the Clinical Center. All patients will undergo the previously described pulmonary vein isolation procedure (PVI). Pulmonary vein entrance block at the end of the ablation procedure should be confirmed and is defined as loss of pulmonary vein potentials using standard techniques.

After PVI and PV entrance block have been confirmed, fibrosis-guided ablation will ensue. The operator will encircle by ablating at the perimeter of the fibrosis and ensure loss of capture in the fibrotic isolated area at 10 milliamp stimulation, and/or completely cover all fibrotic areas with ablation lesions. The tagged ablation lesions should confirm encircling and/or covering of the entire contiguous fibrotic areas indicated by the mapping system. Ablation to the fibrotic areas should be performed as per the operator's standard point lesion energy delivery strategy. It is suggested that a minimum of 8-10 s (and if available 10 g of force) lesions should be delivered. It is recommended that energy delivery (power and temperature) should be adjusted as needed when ablating within the posterior wall region over the region of the esophagus. The operator may connect 2 neighboring fibrotic areas or anchor fibrotic area to anatomic structure such as the isolated PV or valve annuli to avoid creating slow conduction zones or unanchored islands of fibrosis that might be deemed to be potentially arrhythmogenic.

Guidelines for fibrosis-guided ablation are shown in [Figure 6 on the facing page](#) for dense localized fibrosis, and in [Figure 7 on page 22](#) for extensive posterior or anterior wall fibrosis.

In case of cryoballoon ablation, further ablation to cover areas of atrial fibrosis should be guided by the 3D mapping system, intracardiac echocardiography, or fluoroscopic landmark. The duration of freezing targeting fibrotic areas will be left to the discretion

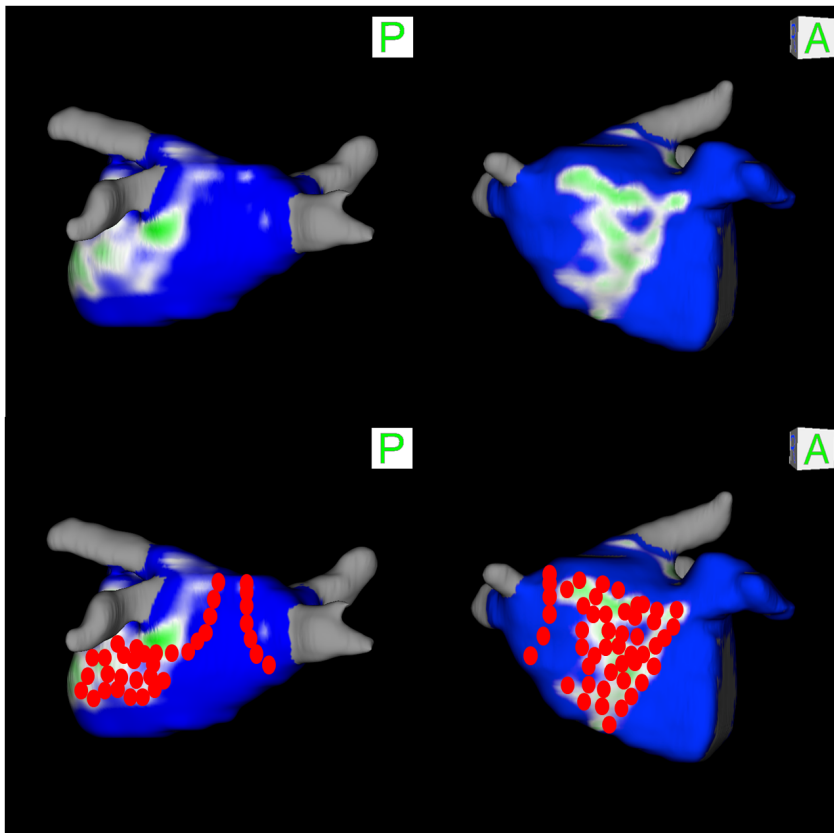


Figure 6: Ablation strategy for dense localized fibrosis.

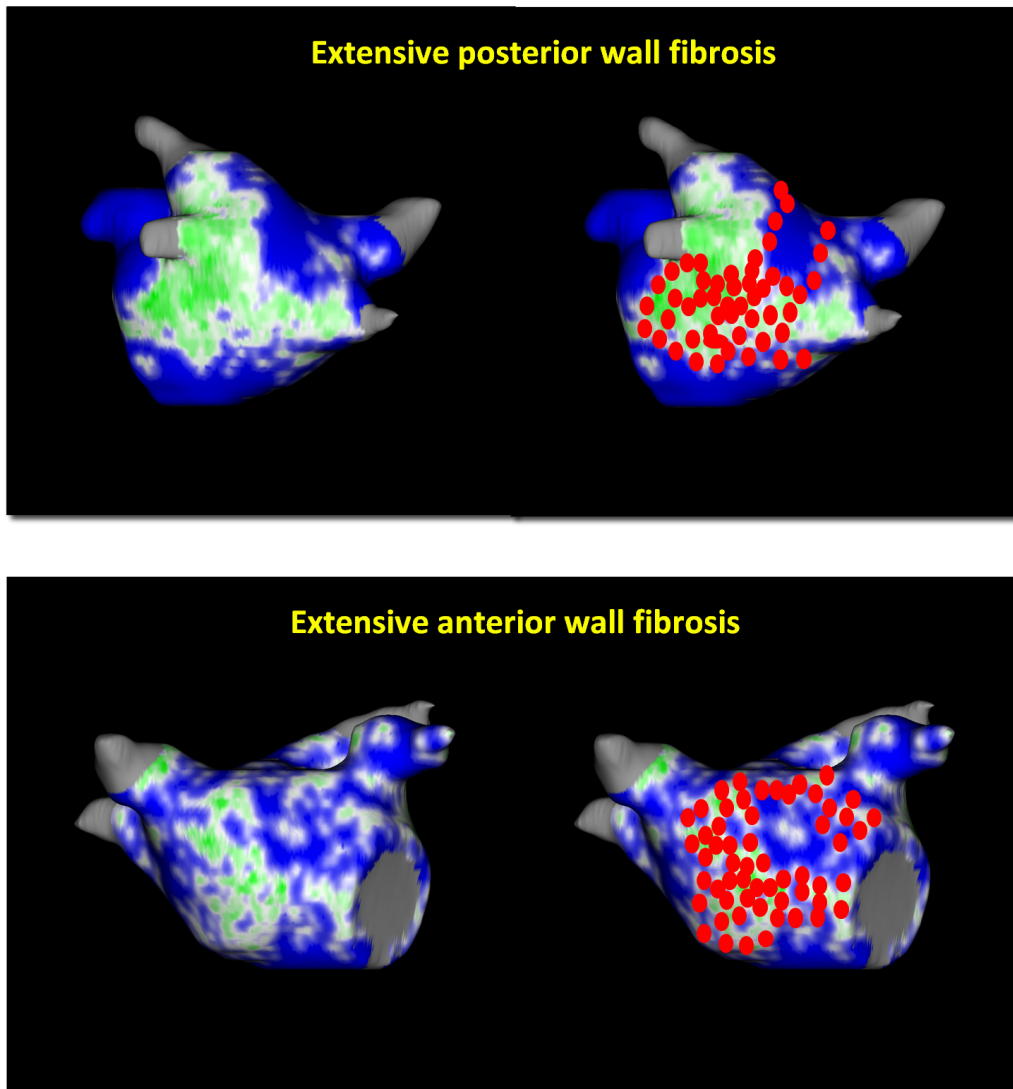


Figure 7: Ablation strategy for extensive fibrosis.

of the operator.

If the normal sinus rhythm cannot be restored after PVI and ablation of fibrotic areas followed by cardioversion in patients randomized to the fibrosis-guided ablation group (Group 2), the operator may to pursue further measures to eliminate recurrent arrhythmia, as described above for the conventional ablation group (Group 1).

To assess ablation procedure protocol compliance, an expert subcommittee will review images of areas of the heart which are ablated for patients in both treatment groups to determine compliance to the ablation protocols using a standardized assessment process. The resulting compliance measures will be compared between treatment groups to verify that the operators targeted appropriate areas based on the patients randomized treatment assignment.

4.7.5 Anti-Arrhythmic Drugs

Clinicians are encouraged to discontinue the use of anti-arrhythmic drugs after the 90-day blanking period.

4.7.6 Repeat Ablation Procedures

In accordance with current standard of care, repeat ablations are discouraged during the blanking period. Following the 90 day blanking period, repeat ablations should be performed using a method preferred by the operator.

4.7.7 Clinical Follow-up

Clinical Center staff will continue post-procedural care following standard of care procedures. Patients will be scheduled for a follow up visit in the 4th month after ablation (between 90 and 120 days post ablation). A post-ablation DE-MRI will be completed to document post-ablation fibrosis coverage and to detect and quantify ablation-related scar formation. Images that do not meet quality standards will not be processed and will be returned to the site. If the post-ablation MRI scan does not meet quality standards, the site physician should repeat the post-ablation MRI scan and re-submit it for evaluation.

5 Study Data

The Clinical Center investigator or delegated study staff will screen subjects for eligibility. For subjects that meet inclusion criteria, the Clinical Center staff will enter the specific exclusion criteria into the database. If the patient is ineligible at this point, no further data will be recorded and the patient will not be approached.

5.1 Pre-Treatment Data

Pertinent review of systems findings will be recorded and this historical information will be used to determine whether subsequent events are different from baseline. This is relevant to adverse event reporting.

5.2 Ablation Procedure Data

Ablation procedure data from the 3D mapping system used the ablation procedure at the study center (e.g. CARTO, Biosense Webster, Ensite NavX, St. Jude Medical, or Rhythmia, Boston Scientific) will be exported and backed up following the procedure and submitted on a regular basis to the DCC for storage and analysis. Sites will use their existing mapping systems during the study. Use of Rhythmia is discouraged unless this is the only mapping system available at the clinical site. Due to the volume of sites and patients, mapping systems, CARTO and Ensite Navx, will be utilized in at least 50 study patients.

5.3 Study Data Elements

We will be collecting data from medical records including demographic information, medications, medical history, lab results, and other relevant clinical data. In addition, we will be collecting data acquired from ECG, MRI, and electrophysiological output devices, reported data such as hospitalizations, adverse events, illnesses, medication changes, clinic visits, and subjective measurements such as quality of life and symptoms of illness.

5.4 ECG Data

5.4.1 ECG Data Collection using *ECG Check* and Other Available Studies

Enrolled patients will transmit *ECG Check* data regularly to the ECG analysis center, which has the capability to read, interpret and store ECG tracings. At the time of enrollment, the Clinical Center personnel will assign each patient a unique identifier. This identifier will be entered into the *ECG Check* device at the participating site by research personnel so that the patient's ECG transmissions will always be associated with their study ID. Patients will be instructed to record their ECG daily, and transmissions of the *ECG Check* data will be sent automatically to the ECG analysis center. ECGs will be reviewed and rhythms will be identified by trained experts blinded to treatment arm assignment. The ECG analysis center will send data regularly to the DCC for data analysis and storage purposes.

Any available data from 12-lead ECGs, Holter monitors, or other continuous monitoring devices will be transmitted to the DCC for inclusion in the study database. These types of studies will not be transmitted to the ECG analysis center for review; rather, such studies obtained in association with a study outcome will be read by an independent

expert to verify the presence of atrial arrhythmia. This expert will be blinded to study arm. In cases where a Holter or other continuous heart monitoring device was done as part of standard of care site staff will upload the summary report to the study database.

5.4.2 Definition of Study Outcome using *ECG Check* and Other Available Studies

For data obtained through the ECG check device the study outcome is formally defined by at least two consecutive, valid ECG tracing indicating an atrial arrhythmia (AA)(atrial fibrillation, atrial flutter or atrial tachycardia). The tracing must be completed after the 90-day blanking period, and demonstrate an atrial arrhythmia. If a second, consecutive ECG Check reading obtained at least 6 hours but no more than 7 days of each other demonstrates an atrial arrhythmia after the first recording the DCC system will notify the Clinical Center that the study's primary AA recurrence outcome has been reached.

It is expected that the majority of enrolled patients who reach the primary study outcome will do so due to two consecutive ECG Check tracings demonstrating AA as above. However, the occurrence of a single positive reading obtained on a 12-lead ECG or Holter monitor or other continuous heart monitoring device will suffice to meet the primary outcome.

In the possible scenario where a repeat ablation is performed after the 90-day blanking period, but there is no AA recurrence demonstrated by an ECG measure (12-lead ECG, ECG Check or Holter monitor or other continuous heart monitoring device), AA recurrence will be inferred for the purposes of the primary study analysis and assigned to the date of the repeat ablation.

The DCC will send notification of the subject having met the primary study outcome to the Clinical Center. The Clinical Center clinician may follow up with the patient based on local standard of care or clinician judgment.

5.5 Symptom Reporting and Quality of Life

At baseline, 3 month, and 12 month clinic visits, participants will complete the University of Toronto AFSS¹¹ and SF-36 questionnaires.

5.6 Database Lock

After the last subject accrual and follow-up visit, the database will not be able to be locked until all data queries have been resolved. Quantitative data will be examined statistically, prior to locking the database. When all such verifications have been completed, the database will be locked prior to undertaking the final data analyses for the study.

6 Statistical Analyses and Power

6.1 Analysis Populations

Randomized Study Population. The randomized study population consists of all randomized patients, irrespective of whether the patient receives an ablation procedure or remains in the trial at the close of the blanking period.

Modified Randomized Study Population. The modified randomized study population consists of all randomized patients who receive an ablation procedure, irrespective of whether the patient remains in the trial at the end of the blanking period.

Safety Population. The safety population consists of all randomized patients who receive an ablation procedure.

Modified Intent-to-Treat Population. The modified intent-to-treat population consists of all randomized patients who receive an ablation procedure and remain in follow-up at the close of the 90-day blanking period.

Unless indicated otherwise, all statistical analyses of efficacy outcomes will be performed in the modified intent-to-treat population and all analyses of safety outcomes will be carried out in the safety population.

6.2 Descriptive Analyses of Baseline Characteristics

Descriptive summaries of baseline clinical and demographic characteristics will be provided by randomized treatment assignment for each analysis population. Baseline characteristics will also be summarized by randomized group in the modified intent-to-treat population for each clinical center and region. In the event that substantial imbalances in particular factors between the randomized treatment groups are detected, sensitivity analyses will be performed after adding these factors as covariates to the Cox regression used for subsequent analyses.

6.3 Primary Analysis of Atrial Arrhythmia (AA) Recurrence

The primary efficacy analysis will be performed in the modified intent-to-treat population using a stratified log-rank test to compare the time to the first AA recurrence after the blanking period between the randomized treatment groups. The log rank test will be stratified by Utah Stage (separate strata for Utah stages I - II, and III - IV). Follow-up will be censored at loss-to-follow-up or death. The primary analysis will be performed with a 2-sided significance level (α) of 0.05.

An associated Cox proportional hazard regression analysis with the same stratification factors will be performed to estimate the hazard ratio between the fibrosis guided ablation and conventional ablation groups with its 95% confidence interval. The possibility that the hazard ratio for treatment assignment varies over the follow-up period (non-proportional hazards) will be investigated by smoothed Schoenfeld residual plots and by performing time-dependent Cox regressions including interaction terms between treatment assignment and follow-up time.^{12, 13} Cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group using a competing risk framework.^{14, 15}

6.4 Components of AA Recurrence

The frequencies and proportions of patients experiencing each of three components of the primary AA outcome:

- atrial fibrillation
- atrial flutter
- atrial tachycardia

will be tabulated by treatment group. As in the primary analysis, only events occurring after the end of the blanking period will be counted in these analyses. Cox regression analyses in which the baseline hazard function is stratified by Utah stage and region will be used to obtain estimates of cause-specific hazard ratios and associated 95% confidence intervals to compare the three components of the primary outcome between the randomized treatment groups. Cumulative incidence curves will be constructed for each of the three components and death under a competing risk framework.^{14, 15} The same analyses will also be performed for symptomatic AA and for symptomatic AA requiring treatment. Because these analyses of the components of the primary endpoint are explanatory, no adjustment for multiple comparisons will be performed.

6.5 Subgroup Analyses of AA Recurrence

Stratified log-rank tests and Cox-regressions similar to those described for the primary analysis will be used to compare the fibrosis guided ablation and conventional interventions in subgroups defined by baseline fibrosis $<$ or \geq 20%. The log-rank test and Cox regression in the fibrosis $<$ 20% subgroup will be stratified by Utah Stages I and II, while the analyses of the fibrosis \geq 20% subgroup will be stratified by Utah Stages III and IV. These analyses will be repeated for the three components of the primary outcome.

6.6 Within-Treatment Group Analyses of AA Recurrence

Cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group separately for each of the four Utah stages in order to estimate the proportions of subjects reaching these events by 1 year within each Utah stage.

Separate Cox regression models using cubic splines for percent fibrosis will be used to relate the hazard for AA recurrence to the pre-ablation percent fibrosis within each randomized group. Similar Cox regressions with cubic splines will be performed within each randomized group to relate the hazard for AA recurrence to the percentage of fibrosis which is covered by the ablation procedure.

6.7 Main Secondary Efficacy Outcome

Quality of life as measured by the Toronto Atrial Fibrillation Burden Scale will be treated as the main secondary efficacy outcome. The main secondary analyses will estimate the effect of the treatment on the mean Toronto Atrial Fibrillation Burden Scale at months 3 and 12 under a mixed effects model in which the baseline Toronto Atrial Fibrillation Burden Scale, visit month (treated as a categorical variable) and the interaction between treatment and visit month are included as fixed effects. An unstructured covariance model will be used to account for serial correlation across the follow-up visits. The main contrast for testing the effect of the treatment will compare the adjusted mean Toronto Atrial Fibrillation Burden Scale at month 12 between the guided ablation and usual care groups. A secondary contrast will compare the adjusted mean Toronto scores at months 3 and 12 between the guided ablation and usual care groups.

6.8 Additional Efficacy Outcomes

Stratified log-rank tests and associated Cox-regressions will also be used to compare initial occurrences of

- a composite outcome including AA recurrence and prescription of an anti-arrhythmic medication,
- stroke,
- cardiovascular hospitalization,
- a repeat ablation,
- AA recurrence following repeat ablation

between the randomized treatment groups. The analysis of repeat ablations will evaluate the time from the end of the blanking period to the first ablation performed after the close of the blanking period. The analysis of AA recurrence following repeat ablation will evaluate the time from the end of the blanking period to the first AA recurrence following the first repeat ablation. If the patient has an AA recurrence after the blanking period but does not have a repeat ablation, the outcome for this analysis will be defined as the initial AA recurrence after the blanking period.

Mixed effects analyses similar to those described for the Toronto scores will be performed to compare the physical and mental composite scores from the SF-36 between the randomized group at months 3 and 12, with primary emphasis given to the month-12

comparison.

AA burden will be estimated for each month of follow-up for each subject as a time-weighted average of the proportion of *ECG Check* readings during that follow-up month which indicate the presence of AA. Generalized estimating equations with stabilized inverse probability of censoring weights to account for early loss-to-follow-up will be used to compare these proportions between the randomized treatment groups.

6.9 Safety Outcomes

The primary safety *composite* outcome is defined by occurrence of one or more of the following events during the 30 day period following the ablation procedure:

- stroke
- pulmonary vein stenosis,
- bleeding,
- heart failure and
- death.

Additional safety outcomes include each of the individual components of the primary safety composite as well as the occurrence of cardiac perforation or esophageal injury within 30 days of the ablation procedure. The primary safety composite and the other safety outcomes will be compared between the randomized treatment groups among patients in the safety population using Fisher exact tests.

The above endpoints as well as all serious adverse events will be monitored and documented throughout the follow-up period. Additionally, clinical sites will document all cardiovascular, cerebrovascular, and gastrointestinal adverse events (including non-serious adverse events in these categories) which are recorded in the patient record or reported at study visits. The distributions of the duration of the ablation procedure and fluoroscopy time will also be summarized by randomized group. The distributions of the duration of the ablation procedure and fluoroscopy time will also be summarized by randomized group.

Frequencies and proportions of the safety population experiencing each of safety endpoint will also be tabulated in the safety population by randomized group over the full follow-up period, including both the blanking period and the further follow-up after the close of the blanking period. The rates of each safety endpoint (potentially including repeat events in the same patients), expressed as the number of events per 100 patient-years of follow-up, will also be summarized over the full follow-up period.

6.10 Capability of Mobile Health Technology to Follow Patients After Ablation

The number of days with valid *ECG Check* readings will be tabulated weekly for each patient and summarized graphically by treatment group for each week throughout the follow-up period. The proportions of subjects with at least one valid *ECG Check* reading during each week of follow-up will be tabulated and graphically displayed. The largest gap (in days) between successive valid *ECG Check* recordings during the follow-up period will also be computed for each subject and summarized by randomized group.

6.11 Statistical Power and Sample Size

Due to a lower than projected event rate for the primary outcome, the trial design has been amended to stipulate an enrollment target of 900 randomized patients rather than require 517 events. Based on the assumption that 40% of patients will reach outcome events, 900 randomized patients will provide 80% power with 2-sided $\alpha = 0.05$ to detect a hazard ratio of 0.74 (corresponding to a 26% hazard reduction) between the fibrosis ablation group and the conventional ablation group.

The original event driven design is described below:

Using an event-driven design, the trial will proceed until a total of approximately 517 arrhythmia recurrence events are recorded to provide 90% power with a 2-sided Type 1 error of 0.05 to detect a reduction in the hazard rate for arrhythmia recurrence by 25% in the fibrosis guided ablation group compared to the conventional ablation group. The sample size required to achieve 517 events depends heavily on the underlying event rate of AA recurrence in the conventional arm. Table 1 on the facing page summarizes estimates of the fraction of patients reaching AA recurrence provided in recent studies of patients with persistent AF. As will be the case in DECAAF II, the DECAAF I and Scherr et al studies included general populations of persistent AF patients,^{1, 16} while the STAR AF study was restricted to persistent AF patients with ≤ 3 years of sustained AF and atrial diameter < 60 mm [16]. Daily monitoring by the *ECG Check* is expected to provide a higher event rate than observed in DECAAF I and in Scherr et al, in which monitoring was performed at a limited number of follow-up visits, and the inclusion of subjects with of sustained AF ≥ 3 years and atrial diameter ≥ 60 mm may lead to a higher event rate than observed in the STAR AF trial.¹⁷ Based on these considerations, the 1-year atrial arrhythmia recurrence probability is projected to fall between 0.50 and 0.70, and a 1-year atrial arrhythmia recurrence probability of 0.60 is used for initial projections of the required sample size.

A total sample size of 888 randomized patients is expected to provide the required 517 events under the following assumptions:

- 60% of conventional ablation subjects have AA recurrence by 1 year after ablation (9 months after the end of the blanking period), and 68% have AA recurrence by 18 months after ablation; and
- the AA recurrence event rate will be reduced by 25% in the fibrosis-guided ablation

Table 1: Estimated recurrence rates for persistent atrial fibrillation.

Study	Sample Size	Monitoring	Specific outcome	Reported Event Rate	Estimated Proportion of Subjects with Events by 1 year
DECAAF I ¹	75	Holters and 12 leads at 3 mos, 6 mos and 1 yr	AA recurrence	36.4% at day 325 after blanking period	36.4% (applies day 325 event rate to 9 months)
STAR AF ¹⁷ (All 3 treatment arms)	589	Holters and 12 leads at 3,6,12, and 18 months + Weekly trans-telephonic monitoring	AA recurrence	59.9% at 18 months after ablation not counting use of anti-arrhythmic drugs	51.3%*
			AA recurrence or use of anti-arrhythmic drugs	67.9% at 18 months after ablation with arrhythmia recurrence of use of anti-arrhythmic drugs	59.3%*
STAR AF ¹⁷ (Isolation Alone arm only)	67	Holters and 12 leads at 3,6,12, and 18 months + Weekly trans-telephonic monitoring	AA recurrence	50.8% at 18 months after ablation not counting use of anti-arrhythmic drugs	42.8%*
			AA recurrence or use of anti-arrhythmic drugs	59.0% at 18 months after ablation with arrhythmia recurrence of use of anti-arrhythmic drugs	50.4%*
Scherr et al ¹⁶	150	Holters at 1,3,6,12 months	AA recurrence	64.7% 1 year after ablation	64.70%

* Assumes 60% lower event rate after year 1 than during year 1.

- group compared to the conventional ablation group; and
- 3% of subjects are lost during the 90 day blanking period, and 0.45% of subjects subsequently die or are lost to follow-up per month; and
- patients are accrued uniformly over a 12-month accrual period, this being a conservative estimate; and
- follow-up will extend for 18 months following each patient's ablation procedure or until a common administrative censoring date 12 months after the ablation procedure of the final randomized subject, whichever comes first; and
- two interim analyses are performed after approximately 1/3 and 2/3 of the total projected number of events have been observed using an O'Brien-Fleming type stopping boundary.

Interim assessments of the actual accrual and event rate (blinded to treatment assignment) will be used to modify the actual number of randomized patients above or below 888 patients in order to assure that approximately 517 AA recurrence events are observed. The projected number of required patients would be 744 if the AA recurrence percentage is 70% at 1 year and 1061 if the AA recurrence percentage is 50% at 1 year.

6.12 Interim Analyses

Interim analyses will be carried out after approximately 1/3 and after approximately 2/3 of the projected total number of events have occurred to guide the Data Safety and Monitoring Board in determining if the trial should be terminated early either due to clear evidence of a benefit of one of the treatment goals, or to a near-0 conditional probability (futility) that the trial would be able to establish a benefit of one of the interventions on scheduled completion. Reports will include adverse events, unanticipated problems, and study outcome results. The α spending function approach of Lan and DeMets¹⁸ will be applied under an approximate O'Brien-Fleming boundary to guide early termination due to efficacy. Futility will be assessed using conditional power calculations.

7 Data Management

7.1 Clinical Sites

Study data may be recorded on paper forms, or directly entered into the electronic data capture (EDC) system. Paper forms will be retained at the Clinical Center and data will be entered by Clinical Center staff into the EDC system provided by the DCC at the University of Utah School of Medicine. The investigator at each participating Clinical Center is responsible for all aspects of study implementation, including MRI procedures, ablation procedures, subject follow-up, collection of accurate study data, and correct entry of the data into the data collection system. These tasks may be specifically delegated to other individuals at the Clinical Center, but the Clinical Center investigator is responsible

to supervise all aspects of the study, and is responsible to assure that all staff involved in this study are adequately trained to perform the delegated tasks.

7.2 DECAAF-II Data Coordinating Center

Clinical data will be entered and securely stored using a secured web-based EDC and database at the DECAAF-II Data Coordinating Center (DCC) which will be at the University of Utah Department of Pediatrics.

7.2.1 Facility, Hardware, Storage, Data Backup and System Availability

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center. The data center facility supports more than 1400 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The data center was built using high industry standards in energy efficient cooling solutions, redundant power systems and fire suppression systems. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

The data center is an entirely virtualized environment. The virtual environment consists of more than 250 virtual servers and nearly 20 physical servers. The data centers virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware or software.

The data center has highly efficient storage resources supporting its virtual environment allowing management of over 65 terabytes of data. Implementing a storage area network (SAN) system to support the virtualized environment provides several benefits:

- storage architecture supports the management of more data;
- performance is better than with non-networked architectures;
- tiered storage is available;
- provisioning and reclamation of SAN disk will be much easier; and most important,
- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Full backups are taken off site on a weekly basis to an off-site commercial storage facility.

Our information systems are available 24 hours a day, 7 days a week to all users outside of scheduled maintenance. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

7.2.2 Security, Support, Encryption and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. User authentication is centralized with four Windows domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using transport layer security (TLS) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the TLS protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with a role based access approach to security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with role based access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

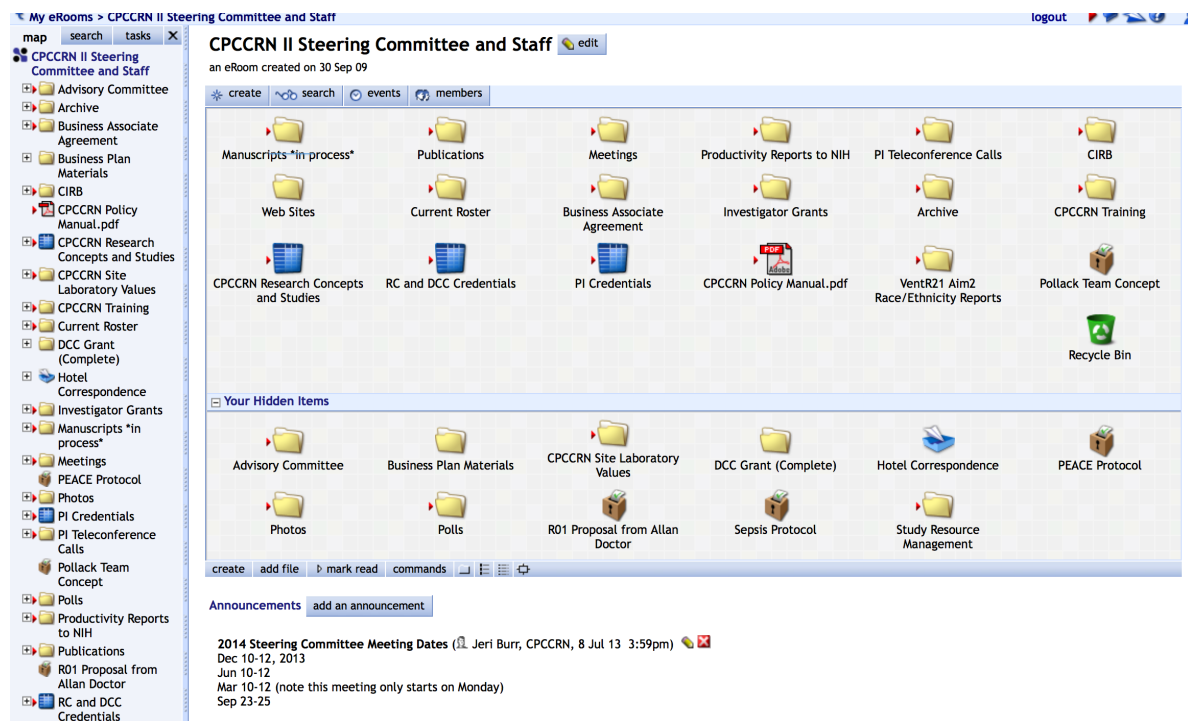


Figure 8: Example Network Steering Committee eRoom

The European Union (EU) has stringent regulations regarding data and patient protection. The Data Coordinating Center (DCC) and the European sites will abide by these regulations.

7.3 Major DCC Software Resources

Extensive software resources are available to support the DECAAF-II study. These include support for electronic collaboration using eRoomTM, database and data warehouse software, clinical trial software, Web server software, our query management system, statistical software, videoconference software, on-line training software, and extensive reporting capabilities.

7.3.1 Electronic Collaboration Support: eRoomTM

We use eRoomTM to provide a “digital office” to support secure, confidential communication and collaboration among multiple users. The software is Web-based and uses an office metaphor of rooms that may contain folders, documents, task lists, calendars, and task oriented databases (Figure 8). The software is highly secure, and management of documents is very intuitive.

The user can drag documents to and from their own desktop directly into the eRoomTM system. The system is optimized to integrate with standard office applications. We

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a database created by  David Nilson on 12 Jan 07

new entry show search (all 8 entries shown)

Below is a list of the CPCCRN Sites and their IRB status.

	Site	Original Approval	Amend v1.13	Amend v1.14	Amend v1.15	#1 Renewal	Amend v1
	Seattle Children's Hospital	11 Apr 08 (v1.14)	N/A	N/A	11 Apr 08	09 Apr 09	11 Apr 08
	Children's Hospital of Los Angeles	19 Jun 08 (v1.14)	N/A	N/A	19 Jun 08	15 Apr 09	19 Jun 08
	Arkansas Children's Hospital	07 Nov 07 (v1.10)	07 Nov 07	07 Nov 07	10 Apr 08	01 Oct 08	01 Oct 08
	Children's Hospital of Michigan	21 Mar 08 (v1.13)	N/A	21 Mar 08	21 Mar 08	12 Mar 09	21 Mar 08
	University of Pittsburgh Medical Center	14 Mar 08 (v1.14)	N/A	N/A	14 Mar 08	20 Aug 08	14 Mar 08
	Children's National Medical Center	01 Apr 08 (v1.13)	N/A	01 Apr 08	01 Apr 08	06 Feb 09	01 Apr 08
	University of California Los Angeles	21 Aug 08 (v1.13)	N/A	N/A	21 Aug 08	05 Mar 09	05 Mar 09

Figure 9: Managing scanned documents with eRoomTM

have used eRoomTM to support all aspects of coordination since inception of our first research network, including coordination of the Steering Committee and subcommittees, preparation of protocols, grants, manuscript preparation and publication, tracking IRB applications and approvals, and storage of scanned regulatory documents. For example, in Figure 9, each underlined entry links directly to a scanned copy of the IRB document, providing the DCC and the funding agency with thorough documentation and continuous access to required documents.

The eRoomTM is also used for organization of materials for individual research projects (Figure 10 on the next page). When the user logs into the system, a listing of eRooms available to that user is displayed (Figure 10a), from which the user can click on the selected study eRoom (examples are shown for the LAPSE (Figure 10b) and Trichotomous Outcome (Figure 10c) studies that are being conducted in one of our NIH funded networks). This provides significant efficiency, as it eliminates printing and mailing of large amounts of paper documents. The system allows us to automatically notify study personnel of protocol changes, updates to Manuals of Operation, and important communications within the any individual project. Investigator and research coordinator acceptance of eRoomTM has been enthusiastic and uniform in the eight current networks that we support.

7.3.2 Database Software

We use Microsoft SQL Server as our primary relational database engine, and have extensive experience (over 20 years) accessing the database from SASTM, Microsoft Access, PHP, Python, Perl, Java, and JavaScript. Microsoft SQL Server provides sophisticated security facilities. We support a number of large databases (tens of millions of records) used for research in the Intermountain Injury Control Resource Center (IICRC), in addition to supporting the network studies. The databases are not directly accessible from outside the offices of the DCC unless a VPN connection is established.

Several of our networks have implemented registries. To enable investigator access to these registries, we create an On-Line Analytical Processing (OLAP) data warehouse

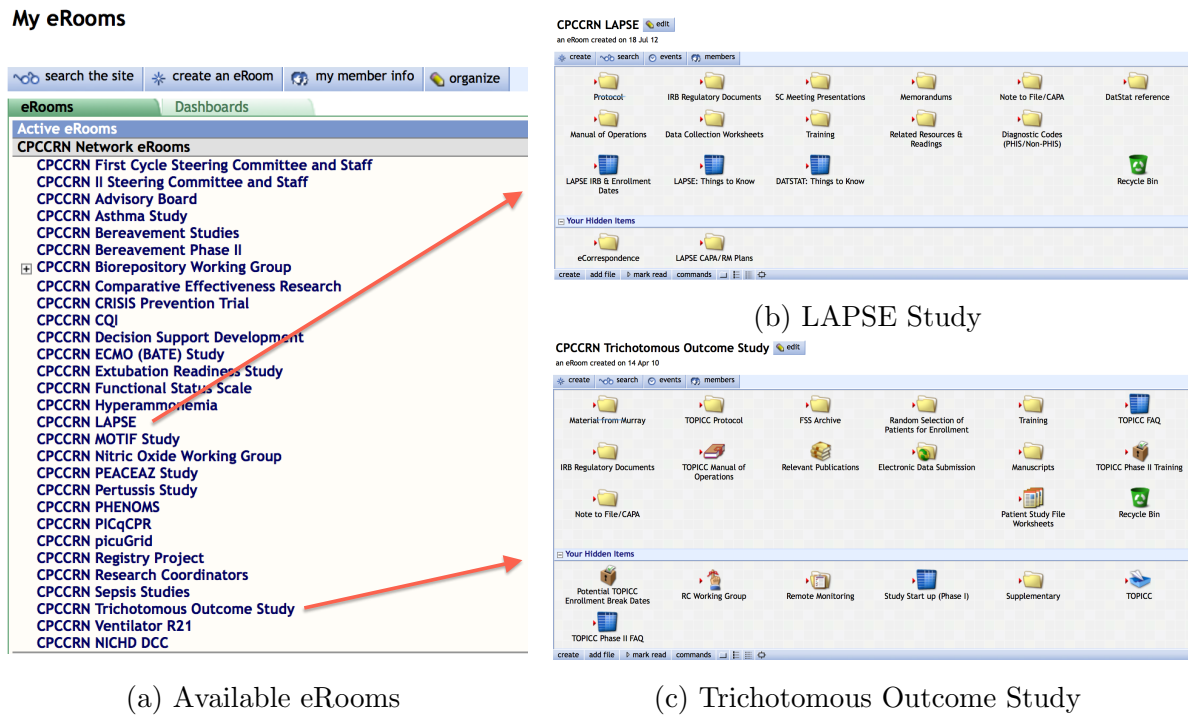


Figure 10: Example network study eRooms.

that permits investigators and DCC staff to easily determine how many patients might be available for future network projects. For example, the NICHD-funded CPCCRN database includes 126,919 PICU admissions for 91,526 different children, and the records are preprocessed so that queries provide near-instantaneous responsiveness.

The user is given a list of dimensions (Figure 11a on the following page) by which they can analyze the chosen measure, which may either be individual patients or PICU admissions. By selecting the site and year, the numbers of patients available each year in each site is instantly displayed (Figure 11b on the next page). Replacing the site dimension with the Major Diagnostic Category (MDC) and restricting to the top eight categories yields numbers of patients within each MDC by year (Figure 11c on the following page). This data warehouse is used extensively by network investigators and DCC staff, and has been extremely useful for providing initial feasibility data for network study concepts.

7.3.3 Clinical Trial Software: OpenClinica

The DCC uses an open source clinical trial data management system called OpenClinica. The backend database is PostgreSQL, an open source, high performance database. OpenClinica allows DCC staff to construct studies conceptually, and it then automatically generates the Internet Web pages (an example is shown in Figure 12). It supports sophisticated skip patterns, field validation, alerts, and range checks. It also maintains an audit of all changes in data fields. Reports can be generated at the DCC, and there is an

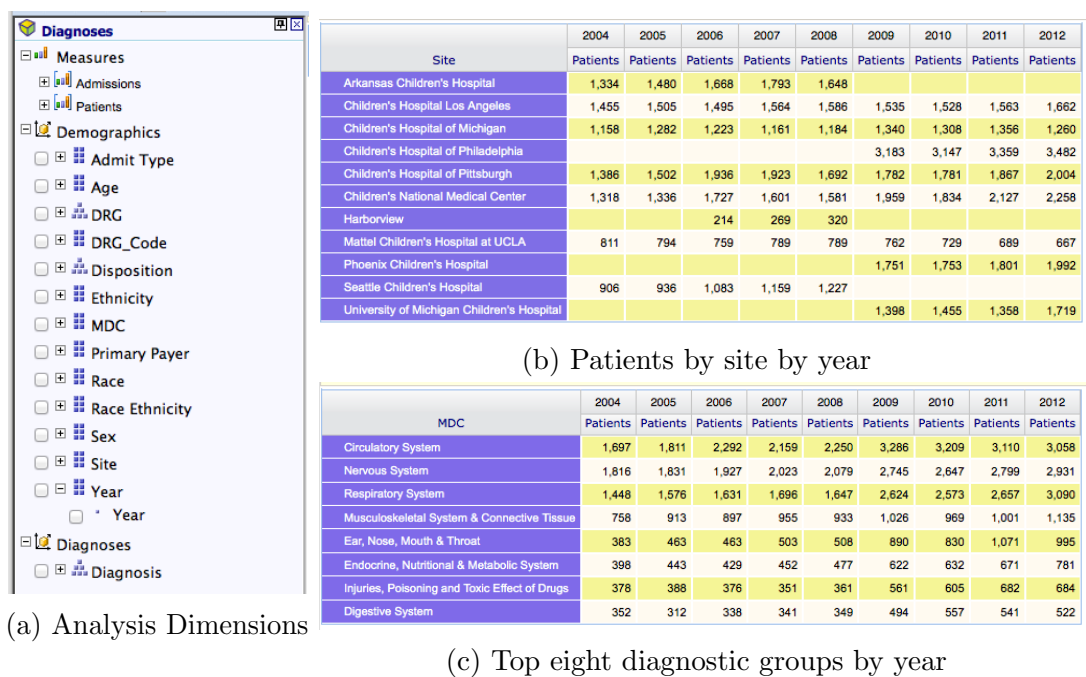


Figure 11: Network Registry data warehouse.

automated extraction function that produces SAS files with formatting statements, using CDISC industry standard ODM output.

OpenClinica is used as a Web-based tool for data entry, but the trial databases are maintained in Microsoft SQL Server, as described earlier. We have developed software that automatically builds a data warehouse for all supported studies at midnight, extracting data from the PostgreSQL database used by OpenClinica, and all daily activities are based on this warehouse. This eliminates problems with on-going data entry and potentially confusing changes in the database if investigators receive data at different times during the day. All reports from the database include an indication of the database snapshot from which the reports are generated. Data that are collected by direct importation from other databases, such as is proposed in Specific Aim Three, are directly placed in SQL Server, skipping OpenClinica. This approach is also used for importing data from other laboratories, such as biomarker measurements, to avoid using Web based data entry that requires human interaction.

While OpenClinica is open source, it is also backed by a commercial company (OpenClinica, LLC) and the DCC purchases support from the company to assure that our server instance meets regulatory validation and receives continuous updates.

Title: Daily Infection Information

Study date: (DD-MMM-YYYY)

Was the patient separated from ECMO on this study day?
 If yes, provide information on the cannulation characteristics form

Was a new culture- or PCR-proven infection diagnosed on this study day?
 If yes, provide details below

Specimen collection date (DD-MMM-YYYY)	Specimen collection time (HHMM)	Upload report
<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="button" value="Click to upload file"/>

Figure 12: Sample Web page of clinical trial software.

7.3.4 Web Server Software

The DCC currently hosts Internet Web sites for CPCCRN (Figure 13 on the next page), PECARN, THAPCA, the Intermountain Injury Control Research Center (IICRC), the National EMSC Data Analysis Resource Center (NEDARC), the Utah State Trauma Registry, and the National EMS Information System Technical Assistance Center. We host these sites with Microsoft Internet Information Services (IIS) or the open source Apache software. Confidential information is not included on these sites because all internal network study communication is done in eRoomTM. The purpose of the public Web site is to inform the public and non-network investigators about the network, providing contact information for potential collaborators.

7.3.5 IICRC Query Management System

While the electronic data capture system (OpenClinica) has data field validation, sophisticated validation of data between different forms requires processing after data are submitted to our site. We have written a Java-based application called the IICRC Query Management System, and use it to manage all queries for studies supported by our staff. For each study, the clinical data manager determines the business rules for each data element, and SQL queries are written to enforce each rule. The system executes during the night, identifies all new data discrepancies, and creates a single email to each site research coordinator that contains all the new discrepancies. Discrepancies are not repeated in email notification for seven days, a feature appreciated by research coordinators. Most importantly, if the data discrepancy is corrected by the site research coordinator, the system automatically resolves the query without requiring DCC staff intervention. If the research coordinator needs to communicate with the clinical data manager and request

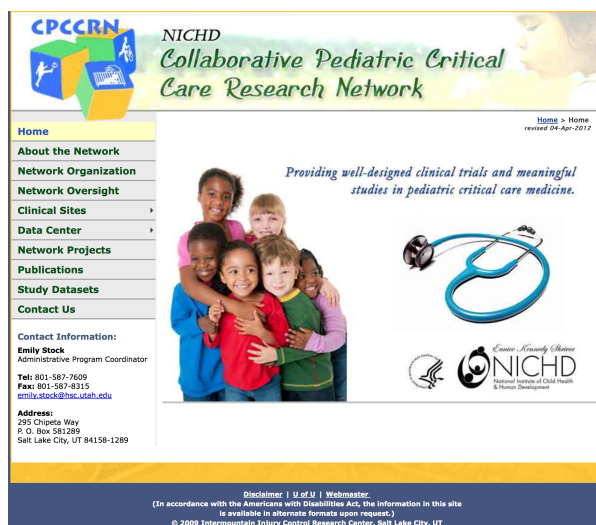


Figure 13: Public Website for CPCCRN

Site ID	Site Name	Aging(days) of Resolved Queries				Total Resolved
		within 7	8 - 14	15 - 21	22 or more	
CHLA	Childrens Hospital Los Angeles	1433	405	269	618	2757
CHOM	Childrens Hospital of Michigan	1750	228	68	328	2420
CHOP	Childrens Hospital of Philadelphia	1875	385	205	701	3181
CNMC	Childrens National Medical Center	2197	261	27	297	2841
UCLA	Mattel Childrens Hospital at UCLA	498	211	95	415	1227
PHNX	Phoenix Childrens Hospital	1655	178	51	329	2233
MICH	University of Michigan Medical Center	1840	307	180	652	2996
UPMC	University of Pittsburgh Medical Center	715	273	143	877	2011
All Site Total		11963	2248	1038	4217	19666

Figure 14: Query System Aging Report of Resolved Queries

manual resolution, this is also done through the system, so a complete audit trail is available for all data element changes and query resolutions.

Supported investigators, research coordinators, and supervisory staff can view real time data quality reports by specific clinical sites or individual query rules, by date of occurrence and resolution, or by aging of queries (Figure 14). This software provides us a powerful management tool for monitoring data quality. Finally, the system maintains an audit trail of all queries, query communications, and query resolution.

7.3.6 Statistical Software

We use SASTM Version 9.1 for most analyses, but also use R and S-PlusTM for selected types of analysis. SUDAANTM is available for longitudinal nested studies. EASTTM

is used for the design and simulation of studies incorporating sequential monitoring designs. The software allows the design of superiority, futility only, and non-inferiority trials, for any type of endpoint, with appropriate adjustment of Type I error and power. Simulations allow comparison of statistical power and other characteristics of competing designs; the interim-monitoring module allows calculation of exact inference at any interim analysis, and facilitates conditional power calculations. We have other specialized statistical software, including StatXact™ (exact statistical methods based on permutation procedures, for small sample categorical and non-parametric data), and LogXact™ (exact small-sample logistic regression).

7.3.7 Webconference Software

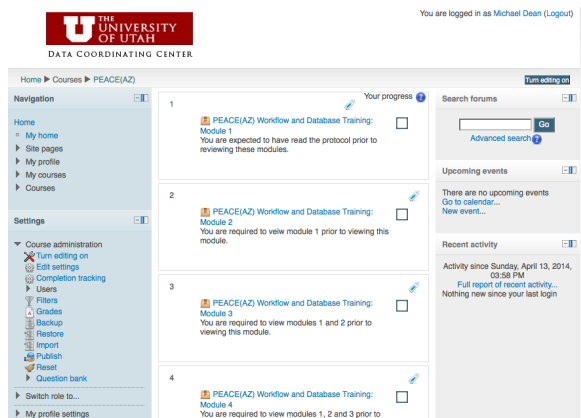
The DCC uses Adobe Connect™ software for web conferences. This software enables us have concept presentations during investigator teleconferences, and facilitates training of research coordinators between Steering Committee physical meetings. We can also record the content of the meetings for later review.

7.3.8 On-Line Training Software

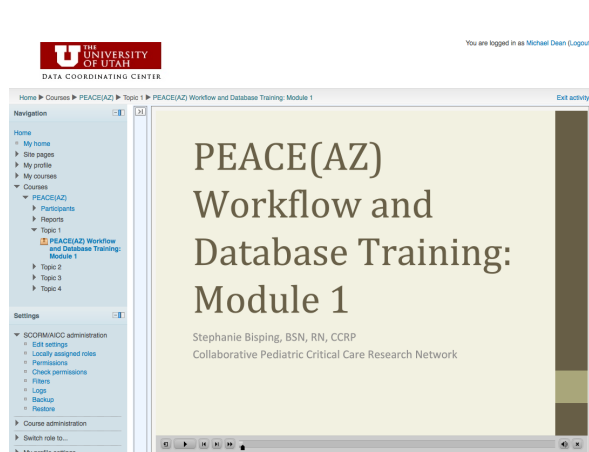
The DCC uses Moodle, an open source free software product to support on-line learning; this software is installed in over 85,000 institutions and has been used by over 65 million users. Moodle includes the ability to provide complete audio recorded presentations. Figure 15a on the next page shows a list of the four modules dealing with workflow in the PEACE(AZ) study being conducted by CPCCRN; the first module is shown in Figure 15b on page 42. The user can start and stop the presentation at will, and at the end of the presentation, a quiz is provided. The software tracks individual users, and certificates are issued when a user has completed all the lessons and passed all the quizzes. We believe that training at Steering Committee meetings is very important, but the on-line training capability is important because of inevitable turnover of research coordinator staff at participating DECAAF-II sites.

7.3.9 Real Time Reporting Software

The DCC uses SharePoint, a secure information sharing platform that enables organizations to manage information and collaboration effectively. The DCC uses SharePoint as the central application that consolidates study data and translates that data into information. Every DECAAF-II investigator, and research coordinator will have accounts for real-time access to network or study level performance metric reports, study demographics, enrollment and data quality reports. In CPCCRN, these are organized through the main site (Figure 16 on the following page), and if the user selects PICqCPR from the list on the left side of the Figure, study accrual information from this study is provided (Figure 17 on page 43).



(a) List of Moodle modules for PEACE(AZ) Study



(b) Module 1 presentation

Figure 15: On-line study training with Moodle system.

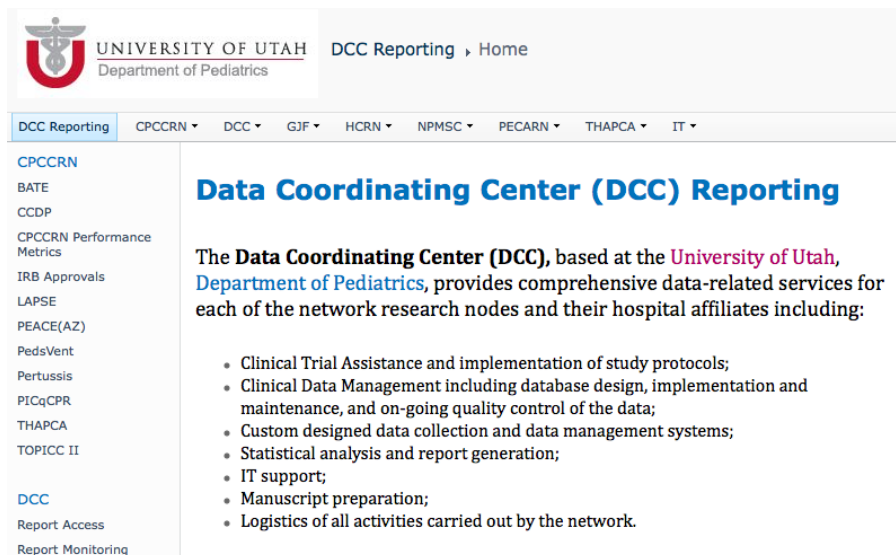
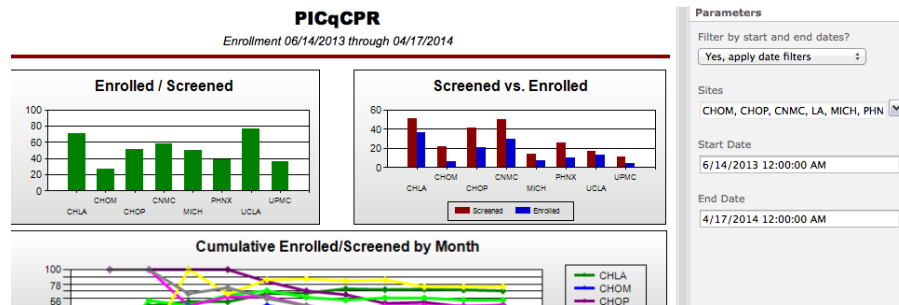


Figure 16: Main reporting page



(a) Graphical display of study enrollment.

Site	IRB Approval	Screened ¹	Enrolled ²	Enrolled / Screened	PICqCPR Event Location ³		
					PICU	CICU	Unknown
CHLA	06/20/2013	51	36	70%	14	22	0
UCLA	06/12/2013	17	13	76%	5	8	0
CHOM	05/10/2013	22	6	27%	6	0	0
CHOP	06/04/2013	41	21	51%	6	15	0
CNMC	06/21/2013	50	29	57%	7	22	0
MICH	05/10/2013	14	7	50%	4	3	0
PHNX	07/08/2013	26	10	38%	5	5	0
UPMC	05/20/2013	11	4	36%	4	4	0
		243	130	53%	51	79	0

1 Screened is defined as the CPR event meeting all inclusion criteria.
 2 Enrolled is defined as meeting all inclusion and exclusion criteria.
 3 PICqCPR Event Location represents enrolled subjects only.
 * Data Last Updated 4/17/2014

(b) Tabular summary of study enrollment.

Figure 17: Accrual report for PICqCPR study.

CPCCRN Study Enrollment Report							
Enrollment 06/12/2007 through 04/17/2014							
Study Site	Study	IRB Approval	Screened	Eligible	Approached	Enrolled ¹	Enrolled / Eligible
CHLA	Critical Pertussis	11/16/2007	NA	11	11	11	100%
	THAPCA	03/26/2009	180	67	64	49	73%
	TOPICCII	06/24/2011	NA	2116	NA	1130	53%
	BATE	11/27/2012	51	NA	NA	50	98%
	PICqCPR	06/20/2013	51	NA	NA	36	70%
	PEACE(AZ)	12/17/2013	NA	NA	NA	0	0%
UCLA	LAPSE	03/06/2014	0	NA	NA	0	0%
	Critical Pertussis	03/13/2008	NA	1	1	1	100%
	THAPCA	04/02/2009	70	24	19	13	54%
	TOPICCII	06/29/2011	NA	830	NA	433	52%
	BATE	12/06/2012	21	NA	NA	21	100%
	PICqCPR	06/12/2013	17	NA	NA	13	76%
	PEACE(AZI)	01/06/2014	NA	NA	NA	0	0%

Parameters

Filter by start and end dates?
 Yes, apply date filters

Sites
 CHOM, CHOP, CNMC, LA, MICH, PHN

Start Date
 6/12/2007 12:00:00 AM

End Date
 4/17/2014 12:00:00 AM

Figure 18: Example site performance summary report.

The default setting for all reports displays all sites and includes the entire duration of each study. Transparency about site performance enables the sharing of best practices from high performing sites, and the opportunity for improvement for sites performing at a lower level. An important feature of these reports is the ability for users to customize the date range and sites included in the report (see right side of Figure 16 on page 42); this allows a site to compare its performance at different time points in a study.

We also provide summary reports to easily assess overall site performance (Figure 18). This report may also be customized by site and date range, enabling DECAAF-II trial staff to identify performance improvement at sites during the studies.

8 Protection of Human Subjects

8.1 Institutional Review Board (IRB) Approval

The Data Coordinating Center (DCC) and each Clinical Center must obtain approval from their respective IRB or Research Ethics Board (REB), or equivalent prior to participating in the study. The Data Coordinating Center will track IRB approval status at all participating Clinical Centers. The DCC will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

8.2 Informed Consent

Potentially eligible subjects will be approached to discuss participation on the study. Research staff will describe the objectives and procedures associated with the study, the risks, and potential foreseeable risks associated with the research. Research staff at Clinical Centers will obtain the subject's informed consent prior to initiation of study activities. Documentation of consent will be the responsibility of the Clinical Center.

8.3 Potential Risks

Catheter-based atrial fibrillation (AF) ablation is an accepted treatment for atrial fibrillation and is widely used as a treatment for patients with persistent or paroxysmal AF. Subjects in this trial will receive standard-of-care PVI ablation in both treatment arms. The general risks and benefits of catheter-based ablation for AF, e.g. cardiac perforation, pulmonary vein stenosis, stroke, death, and bleeding or pain at the insertion site, are outlined in the standard medical procedure consent forms at respective Clinical Centers.

There are potential risks related to the fibrosis-guided ablation procedures. Due to the longer time under anesthesia, more areas being ablated and longer total procedure time, subjects in the fibrosis-guided ablation group are at greater potential risk for scarring, injury to peri-esophageal vagal nerves, esophageal injury, cardiac perforation, and atrial esophageal fistulas.

Because there are extra potential risks associated with the procedures for the fibrosis-guided ablation, some subjects will be randomized into a group with more overall risk. Agreeing to participate means that subjects are willing to accept the possibility of being exposed to these added risks. This risk is offset in part by the potential benefit from fibrosis-guided ablation, which may provide better clinical outcomes.

Women who are pregnant are excluded from the trial. Premenopausal females will be given a urine pregnancy test before ablation. If a subject becomes pregnant while taking part in the study, the participant will be instructed to immediately notify the research doctor. This situation, though possible, is unlikely since the majority of subjects will be older in age. A pregnancy test is standard of care for pre-ablation procedures and will not be paid for by the study.

The small amount of blood drawn for the study will pose minimal risk e.g. bleeding, pain, or hematoma at the puncture site.

There is minimal risk of accidental disclosure of subject identity and health information.

8.4 Protections Against Potential Risks

The daily ECG transmissions will potentially detect treatment failure faster than routine follow up and will provide additional safety over and above standard of care. The ablation protocols for both study arms are described in this protocol, but these approaches allow for clinical judgment during ablation procedures. Ablation procedures will be guided by the DE-MRI image in the treatment arm, which may result in additional ablation, but clinicians must always exercise judgment in ablation procedures for each subject. Adverse events will be tracked during the study and serious adverse events will be promptly reported to the Data Coordinating Center.

Study information will be kept in a secured manner and the database will be password protected. Loss of confidentiality is mitigated by the use of the Data Coordinating Center which has a highly secure IT infrastructure. Data security is described in Section 7.2.2 on page 34.

8.5 Potential Benefits for Subjects

Subjects receiving fibrosis-guided ablation targeting atrial fibrosis may stay in a normal heart rhythm and may have fewer AA recurrences than those who receive conventional pulmonary vein isolation (PVI) ablation. There is potential for direct benefit for the participants in this study who receive the DE-MRI guided catheter-based ablation.

The study also makes use of new technologies that allow closer and more frequent monitoring of patients' heart rhythm. Subjects in this study, regardless of arm assignment, will receive the mobile heart monitoring device (*ECG Check*) to complete regular monitoring of their heart rhythm after the ablation procedure. This may allow for earlier detection of AA recurrence and may also reveal other arrhythmias of clinical significance. Thus, subjects may experience an enhancement in quality and frequency of monitoring using the ECG device. ECG output will be reviewed regularly by a trained nurse (or other trained individual), and a specified individual at each Clinical Center will be made aware of atrial arrhythmia recurrence that may be considered clinically significant. The Data Coordinating Center will receive regular ECG data transmissions and will automatically notify sites of AA recurrence so that clinicians may contact subjects if they choose. Subjects will be instructed to contact their local physician or local emergency services if they experience any symptoms, as ECGs will not be read in real time.

The second MRI scan will provide information about early post-ablation scar formation and the presence and degree of pulmonary vein stenosis. This information may be clinically beneficial to patients in both arms of the study. For example, it has been shown that post-ablation scarring correlates with procedure outcomes and AF recurrence.^{19, 20} In addition, any progression of PV stenosis confirmed by an MRI scan 3 months post-ablation may be implicated in the future development of severe stenosis.²¹

8.6 Potential Benefits for Future Patients

Future patients with atrial fibrillation will benefit from the study if the results determine that one treatment regimen is superior to others in decreasing the recurrence of atrial fibrillation.

8.7 Withdrawal from Study

A subject may withdraw from the DECAAF-II study at any time. If a subject withdraws permission to continue in the study, all study interventions will be discontinued, but the

medical course of the patient will continue to be followed for adverse events until the patient has reached the administrative endpoint of the study.

9 Data and Safety Monitoring Plan

9.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB). The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as described on page 32. The purpose of the DSMB is to advise the sponsors and Principal Investigator(s) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual Clinical Center, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy.

The DCC will send reports relating to these topics to DSMB members prior to each DSMB meeting. Interim analyses are anticipated after approximately 1/3 and after approximately 2/3 of the projected total number of events have occurred. The DCC will staff the DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by the DSMB Chairperson. These closed minutes will not be available outside the DSMB prior to the end of the study. The DSMB Chairperson will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. The summary will be provided to the DCC, and the DCC will send the summary to all Clinical Center investigators for submission to their respective Institutional Review Boards/Research Ethics Board(s).

9.2 Adverse Event Reporting

Assuring patient safety is an essential component of this protocol. Each participating Clinical Center investigator has primary responsibility for the safety of the individual subjects under his or her care. Clinical visits will occur at months 3 and 12 months. Site staff will also call the subject at 6 Month. For subjects whose follow-up period extends to 18 months site staff will conduct a chart review and call the subject to identify any additional adverse events. Clinical investigators may schedule additional clinic visits according to their standard of care or as needed for clinical reasons. At regular study visits, and at any scheduled or unscheduled visits in the first 30 days, the Clinical Center staff will record all new or worsening symptoms or events as reported by the patient. After the 30 days until the end of study assessment we will collect cardiovascular, cerebrovascular, and gastrointestinal adverse events and serious adverse events. The 2017 HRS consensus statement²² will be used for guidance in capturing these adverse events.

All adverse events meeting these definitions occurring after study randomization through final follow up will be recorded and entered into the electronic data entry system provided by the DCC. In accordance with local IRB/REB requirements, the Clinical Center investigator may be required to report such events to the IRB/REB in addition to notifying the DCC.

9.2.1 Definitions, Relatedness, Severity and Expectedness

Definition: An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. The Clinical Center investigators will evaluate adverse events. Adverse events will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established. Arrhythmias will not require reporting as adverse events because patients will be transmitting daily ECGs using the mobile device, and these will be regularly reviewed and interpreted by the central monitoring team. ECG findings will also be reported to the DCC and recorded in the study database.

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the following criteria. *Relatedness may **not** be assessed by a research coordinator, and must be assessed by an investigator.*

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and *cannot be reasonably explained* by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Seriousness: The severity of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or

- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with atrial fibrillation, ablation procedures, other underlying medical conditions of the subject, is directly related to study outcome, or is otherwise mentioned in the protocol, informed consent, or other study documents.

Expected complications of atrial fibrillation or standard catheter ablation procedures include development of atrial-esophageal fistula or injury, pulmonary vein stenosis, cardiac tamponade, cardiac perforation, esophageal injury, embolic events, stroke, phrenic nerve injury, mitral valve trauma, air embolism, acute coronary artery occlusion, and death. Catheter entry site complications include swelling, bleeding, pain, hematoma at catheter entry site(s).

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

9.2.2 Time Period for Adverse Events

For purposes of this study, adverse events will be recorded for the period following randomization through the final follow up visit.

9.2.3 Data Collection Procedures for Adverse Events

From randomization until 30 -days post-ablation, all adverse events (including serious adverse events), whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. In the time frame 30 -day post-ablation until end of study cardiovascular, cerebrovascular and gastrointestinal adverse events whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the site investigator will assess the severity and relationship to the study. Laboratory values that are abnormal at the time of randomization and that do not worsen will not be recorded as adverse events.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center because this requires specific training.

9.2.4 Unanticipated Problems (UP)

Unanticipated problems (UP) are deemed as incidents, experiences, or outcomes that are unexpected, related to participation in the DECAAF II study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The Clinical Center investigator will report unanticipated problems to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the DSMB in an expedited manner (within 24 hours). In accordance with local IRB requirements, the Clinical Center investigator may be required to report such unanticipated problems to the IRB in addition to notifying the DCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and the DSMB cannot be reached expeditiously, the DCC will notify the study investigator (Dr. Marrouche) and all investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the DSMB.

9.2.5 Monitoring Serious Adverse Events

The Principal Investigator of the Data Coordinating Center (Dr. Dean) will act as the medical monitor for this study. If Dr. Dean is unavailable, a qualified physician will be designated to fulfill this function. Site investigators and/or research coordinators will report serious adverse events to the Data Coordinating Center within 24 hours. A detailed

completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign each SAE report after review. All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by DSMB members.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or the DSMB chairperson cannot be reached expeditiously, the DCC will notify the study investigator (Dr. Marrouche) and all Clinical Center investigators to cease enrollment in the trial. Resumption of enrollment will not occur without the approval of the DSMB.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

After notification of the DSMB chairperson of serious, unexpected, and study-related adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Marrouche) and all clinical investigators, who will be instructed to report this to their local IRB or ethics boards.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

9.2.6 Follow-up of Serious, Unexpected and Related Adverse Events

Serious adverse events, that are unresolved at the time of the patient's termination from the study, will be followed by the Clinical Center investigators until the events are resolved, the subject is lost to follow up, or the adverse event is otherwise explained or has stabilized.

10 Study Training and Monitoring

10.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics including applicable regulations and good clinical practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The DCC, in collaboration with the study investigator (Dr. Marrouche), will be the main contact for study questions.

10.2 Study Monitoring

The investigator recognizes the importance of ensuring data of excellent quality, and site monitoring is critical to this process. We will utilize site monitoring as a part of a risk-based monitoring plan to ensure excellent quality data in the proposed study. Site monitors will monitor enrolling centers during the trial to assess protocol and regulatory compliance as well as data quality. The timing, frequency and method of interim monitoring will be outlined in a separate site monitoring plan. Select sites may be monitored remotely. Remote access monitoring, e.g., gaining access to electronic health records, and consent forms, and regulatory documents may supplement or in some circumstances replace on-site visits for very low enrolling sites. Participating Clinical Center staff must make medical records, regulatory and study documents available to the monitor or DCC staff as requested to assure quality and study protocol compliance. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

10.2.1 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol, will be completed which outlines specific criteria for monitoring of the trial. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review, and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all subjects within a site; key data or all data), the schedule of when these activities are to take place, how they are reported, and a time frame to resolve any issues found. Remote site monitoring data elements and schedule will be determined by the DCC.

10.2.2 Clinical Site Monitoring

Site monitoring visits will be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on risk assessment, budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation call (prior to patient enrollment), interim visits, and a close out call. The site initiation may take place as group training made up of site investigators and research assistants.

10.2.3 Remote Monitoring

The DCC will supplement on-site monitoring with remote monitoring activities. Remote monitoring involves review of the data entered by staff coordinators or physicians and source documents to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record to the DCC staff, who review those materials against the data recorded in the electronic data capture system. Some sites may elect to provide remote access to documents for quality review.

11 Regulatory Issues

11.1 Food and Drug Administration

In this trial, 3 different U.S. Food and Drug Administration (FDA) approved devices will be utilized. All three devices also have a CE- mark and approved in Europe. The first is a hand-held ECG application that transmits the ECG. This device has been approved for the transmittal of ECG information. The second is a software application for viewing and post-processing of cardiovascular MRIs to obtain left atrial enhancement quantification and visualization on a 3D model, which has been previously approved for this indication. Finally, ablation catheters that are used for atrial fibrillation treatment are being used in their approved manner. Although this trial will be the first to use all 3 devices together, this use does not necessitate a new IDE as this composite utilization falls within current approvals for each device for their approved indications.

11.2 Health Insurance Portability and Accountability Act

The abstracted data will include limited identifiers as defined by the Health Insurance Portability and Accountability Act, such as dates of birth and service. Abstracted data will be retained and archived at the Data Coordinating Center in accordance with record retention requires of the Food and Drug Administration and the NIH. Contact information will not be provided to the Data Coordinating Center (it will be provided directly to the central follow up research staff). For data analysis outside the Data Coordinating

Center (e.g., when a public access database is made available), the Data Coordinating Center will create a completely de-identified analytical database for use by the study investigators, and for final archiving. All U.S. study sites have been or will be offered Business Associate Agreements with the University of Utah. Copies of signed Business Associate Agreements are maintained at the Data Coordinating Center.

11.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

11.4 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

11.5 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the the Food and Drug Administration, and the Institutional Review Board (IRB) for each study site.

11.6 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

12 Data Sharing Plan

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health Insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identify of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies to be determined by the DECAAF-II Investigators and sponsors, the releasable database will be provided to users in electronic form. The DCC is able to produce a relational database export, or use SAS or SPSS data sets.

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Summary of DECAAFII Protocol Changes for Version 2.03

1. The appropriate protocol pages were changed to reflect that the Principal Investigator Dr Marrouche moved from the University of Utah to Tulane University.
2. Primary endpoint, design, and statistical changes:
 - a. Definition of primary endpoint was updated to clarify that the occurrence of a single positive reading obtained on a 12-lead ECG or Holter monitor or other continuous heart monitoring device after 90 -days post ablation also would be counted as an AA recurrence.
 - b. Changed the trial design from an event driven trial to targeting 900 subjects
 - c. The process to assess protocol compliance was changed to have an expert subcommittee review all available images of areas of the heart which are ablated for patients in both treatment groups using a standardized assessment process. This was changed from only evaluating a subset of cases from both treatment groups and have these be evaluated by the Steering Committee.
 - d. Cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group separately for each of the four Utah stages in order to estimate the proportions of subjects reaching these events by 1 year. “and by 18 months within each Utah stage” was removed.
3. Adverse event reporting related changes:
 - a. HRS 2017 consensus statement will be used as guidance to capture the adverse events instead of the 2012 HRS consensus statement.
4. ECG Check related changes:
 - a. Tablet computer or iPad 3 or newer devices turned out not to be compatible with the ECG check app and were removed from the text.
 - b. The ECG check device didn't have the capability to notify the patient if a daily transmission was missed. In addition, there was no mechanism that the site coordinator would be notified that the patient stopped transmitting. Therefore, these statements were removed from the protocol.
 - c. Due to technical issues with the app the symptom questions answered by a majority of the subjects were not transmitted. As there was too much missing, this data will not be analyzed.
 - d. The clinical sites only received an alert if an atrial arrhythmia rhythm (atrial tachycardia, atrial fibrillation, or atrial flutter) was detected. The sites were not alerted of other rhythms that may be considered clinically significant as part of the study.
5. MRI related changes:
 - a. The revised protocol allowed the use of the pre-ablation MRI for the ablation up to 90 days, if there were circumstances preventing the ablation to take place within 30 days of the DE-MRI scan.
 - b. It also made the requirement to when the post- ablation scan was obtained less stringent. The window to obtain the MRI was extended from 90-120 days to 90 -180 days after the procedure.
 - c. Clarified that if patient was randomized to PVI arm that the site would receive a blank model.

- d. Use of Rhythmia mapping system was discouraged as not all versions of the 3D mapping system allowed the upload of the 3D model.
6. Duration of study and follow-up:
- a. The estimated duration of the entire study was changed from 3 to 5 years
 - b. As the end of the study was approaching the follow-up duration was shortened from 18 months to 12 months based on the date of randomization. The sites were informed of the shortened follow-up.
7. Lab related changes:
- Not all sites were able to obtain Galectin-3, BNP, or C-reactive protein. The protocol was changed to allow sites to opt out of collecting blood samples for one or more of these tests.
8. Other changes:
- a. The language was revised to reflect the updates to the data systems and security measures in place at the Data Coordinating Center at the University of Utah.
 - b. Updated language to reflect that the site initiation visit was a call and not an actual visit.

DECAAF II SAP FIRST VERSION

STATISTICAL ANALYSIS PLAN

Protocol Title: Efficacy of DE-MRI Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II)

Protocol Version and Date: 2.00; September 22, 2015

SAP Primary Author: Tom Greene

SAP Version 1 Date: March 23, 2016

1 PREFACE

1.1 Purpose of SAP

The Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the Protocol: Efficacy of DE-MRI Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II).

The SAP is important for the following reasons: (1) to ensure that data collected in the study are adequate to address the study hypotheses; (2) to prevent ad hoc decisions in analyzing study data; and (3) to prospectively identify a timeline and structure for completion of study analyses.

1.2 Auxiliary/Other Documents

The following documents were reviewed in preparation of this SAP

- Protocol: Efficacy of DE-MRI Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II)

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of the DECAAF II trial are:

1. to test the hypothesis that patients receiving fibrosis-guided ablation will have fewer AA recurrences than those who receive PVI ablation alone.
2. to test the hypothesis that receiving fibrosis-guided ablation will not be associated with increased rates of peri-procedural complications including stroke, pulmonary venous stenosis, bleeding, esophageal injury, cardiac perforation, heart failure, and death.

2.2 Study Endpoints

2.2.1 Primary Outcome

The primary endpoint is the recurrence of atrial arrhythmia post-ablation, defined as a non-self-terminating bout of atrial fibrillation, atrial flutter, or atrial tachycardia. The primary endpoint will be demonstrated by the occurrence of one of the following events during the study follow-up after the 90 blanking period:

- a) two consecutive, valid ECG tracings obtained between 6 hours and 7 days of each based on either the ECG Check model device, a 12-lead ECG, a 24 Holter or other continuous monitoring device,
- b) a repeat ablation.

It is expected that the majority of enrolled patients who reach the study outcome will do so due to two consecutive ECG Check tracings demonstrating AA as above. However, these same criteria, requiring demonstrated atrial arrhythmia occurrences no less than 6 hours and no more than 7 days apart, will also be applied to any readings obtained from 12-lead ECGs, Holter monitors, or other continuous recording devices. In some instances, this may mean that the study endpoint is achieved from a single monitoring study lasting more than 6 hours. It is also possible that a patient may achieve the study outcome from multiple sources (e.g., a single ECG Check reading of AA followed by a finding of AA from a 12-lead ECG performed 6 hours to 7 days later).

As described in Section 8.2, the primary analysis will compare the time from the completion of the 90-day blanking period to the subsequent occurrence of the primary endpoint between the randomized treatment groups. Any repeat ablations which occur during the 90 day blanking period will not be counted as events, and will not affect the definition of the start of the blanking period which is defined as the date of the initial post-randomization ablation.

2.2.2 Secondary Outcomes

The main secondary outcome is quality of life as assessed by the Toronto Atrial Fibrillation Burden Scale. The main secondary analyses will estimate the effect of the treatment on the mean Toronto Atrial Fibrillation Burden scores at months 3 and 12, with the 12-month comparison receiving primary emphasis in interpretation of the study results.

Additional secondary outcomes will be classified as Category A or Category B secondary outcomes, where outcomes in Category A will be subjected to more extensive statistical analyses than outcomes in Category B. The choice of which outcomes are placed in Categories A and B is based in part of their importance to the study and in part on technical considerations including statistical power, completeness of ascertainment, and measurement error. The designation of these two categories is not specified in the trial protocol, but rather is employed to simplify the description of the statistical analysis plan.

The Category A secondary efficacy outcomes are:

1. The composite of AA recurrence and prescription of an anti-arrhythmic medication
2. Symptomatic atrial arrhythmia
3. Repeat ablation
4. Stroke
5. Cardiovascular (CV)-related hospitalization
6. The RAND SF-36 physical and mental health summary scores obtained at month 3 and month 12,
7. The Toronto Global Well-Being, AF Symptom, and Health Care Utilization scores obtained at month 3 and month 12 during follow-up.

The individual components of the primary outcome:

- atrial fibrillation
- atrial flutter
- atrial tachycardia

will also be evaluated as Category A secondary outcomes.

The statistical analyses of the composite of AA recurrence and prescription of an anti-arrhythmic medication, symptomatic atrial arrhythmia, repeat ablation, and the individual components of the primary outcome will compare the time from completion of the 90-day blanking period to the first occurrence of the indicated events during the subsequent study follow-up between the randomized groups. The statistical analyses of the stroke and CV-hospitalization endpoints will compare the time from the initial ablation procedure to the occurrence of these endpoints at any time during follow-up, including the blanking period. See Section 8.3 for additional details.

The Category B secondary outcomes include:

1. Cardiovascular mortality
2. AA recurrence following repeat ablation

3. Arrhythmias other than AA
4. AA burden, determined for each month of follow-up as the proportion of ECG Check readings during that follow-up month which indicate the presence of AA.
5. The 8 individual SF-36 health subscales: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perception assessed at 3 months and 12 months follow-up the initial ablation procedure.

As with the primary endpoint, arrhythmias other than AA must be confirmed by 2-consecutive valid ECG tracings obtained either by the ECG Check model device, a 12-lead ECG, or a 24-hour Holter or alternative continuous monitoring device. Analyses of cardiovascular mortality will include all cardiovascular deaths during the follow-up period following the initial ablation procedure. Analyses of AA recurrence following repeat ablation and AA burden will be defined using AA-recurrence information during the follow-up subsequent to the 90 day blanking period.

2.2.3 Safety Outcomes

The main safety outcome is a composite endpoint defined by occurrence of any of the following events within 30 days of the ablation procedure:

- stroke
- pulmonary vein stenosis,
- bleeding requiring transfusion,
- heart failure and
- death.

Additional safety outcomes include:

- Each of the individual components of the primary safety composite
- Cardiac perforation within 30 days of the ablation procedure
- Esophageal injury within 30 days of the ablation procedure

SAEs which occur at any time during the follow-up period of the trial will be tabulated in accordance with standard MEDRA classifications. Responses to the 5 symptom questions (chest pain, shortness of breath, racing heart, dizziness/lightheadedness, syncope or any passing out) will also serve as safety outcomes. The analysis of the 5 symptom questions is described in Section 8.3.4.

2.3 Covariates

Because this is a randomized trial, covariate adjustment for baseline characteristics is not necessary to provide unbiased estimates of treatment effect. However, the primary analysis will be stratified by Utah Stage (Utah stage categories I & II vs. categories III & IV), and a number of

the secondary analyses will relate study outcomes to Utah stage or the % fibrosis at baseline, which is the continuous measure used to define Utah stage.

3 STUDY DESIGN AND METHODS

3.1 Overall Study Design

DECAAF II is a prospective, randomized, multi-center trial of patients with persistent AF and presence of atrial fibrosis. Subjects will be randomized to one of two study groups to receive conventional PVI ablation (Group 1) or PVI + fibrosis-guided ablation (Group 2). Details of the two treatments can be found in the Protocol.

3.2 Randomization and Blinding

3.2.1 Randomization

Randomization to each treatment will be in a 1:1 ratio stratified by Utah stage (I-II vs III-IV) and clinical center. Randomized permuted blocks will be used for randomization. This trial will use a web-based system for randomization.

After consenting to participate in the study, the subject will undergo a DE-MRI scan to assess for extent of atrial fibrosis. After the DCC has verified adequate quality of the DE-MRI, study subjects will be randomized to receive PVI alone or fibrosis-guided ablation. The DCC will complete randomization and notify the site no more than 96 hours before the scheduled procedure to allow adequate time for scheduling and preparation.

3.2.2 Blinding

The ablationists for patients randomized to the PVI ablation group will be kept blinded to the pre-ablation MRI fibrosis results. In addition, MRI image processors will be blinded to arm assignment and all readings of the ECG data used to determine the primary outcome will be blinded to the patient's randomized treatment arm. The site PI and staff may be aware of the patient's randomized treatment assignment, but will be instructed to limit the number of individuals aware of the patient's randomized assignment to the extent possible. All reasonable efforts will be made to keep the patient blinded to their randomized treatment assignment.

3.3 Sample Size and Power Determination

Using an event-driven design, the trial will proceed until a total of approximately 517 arrhythmia recurrence events are recorded to provide 90% power with a 2-sided Type 1 error of 0.05 to detect a reduction in the hazard rate for arrhythmia recurrence by 25% in the fibrosis guided ablation group compared to the conventional ablation group. A total sample size of 888 randomized patients is estimated to provide the required 517 events under the following assumptions:

- 60% of conventional ablation subjects have AA recurrence by 1 year after ablation (9 months after the end of the blanking period), and 68% have AA recurrence by 18 months after ablation; and

- the hypothesized relative reduction in the AA recurrence event rate is 25% in the fibrosis-guided ablation group compared to the conventional ablation group; and
- 3% of subjects are lost during the 90 day blanking period, and 0.45% of subjects subsequently die or are lost to follow-up per month; and
- patients are accrued uniformly over a 12-month accrual period; and
- follow-up will extend for 18 months following each patient's ablation procedure or until a common administrative censoring date 12 months after the ablation procedure of the final randomized subject, whichever comes first; and
- two interim analyses are performed after approximately 1/3 and 2/3 of the total projected number of events have been observed using an O'Brien-Fleming type stopping boundary.

Interim assessments of the actual accrual and event rate (blinded to treatment assignment) will be used to modify the actual number of randomized patients above or below 888 patients in order to give high confidence that at least 517 AA recurrence events are observed. The projected number of required patients would be 744 if the AA recurrence percentage is 70% at 1 year and 1061 if the AA recurrence percentage is 50% at 1 year. It is possible that the accrual period may extend more than 12 months; if this occurs the average follow-up time will be increased as a greater proportion of patients would be enrolled at least 18 months prior to the common administrative censoring date for the trial, and the required number of patients may be slightly reduced.

Various approaches, including projections and simulations based on study data observed to date, may be implemented to estimate numbers of events expected in the study population under scenarios where recruitment is stopped at a certain number of patients. Such approaches should again give high confidence (e.g. 95% or greater) that the required number of events will be achieved under realistic study scenarios.

4 STUDY SUBJECTS AND ANALYSIS POPULATIONS

4.1 Analysis Population

Randomized Study Population. The randomized study population consists of all randomized patients, irrespective of whether the patient receives an ablation procedure or remains in the trial at the close of the blanking period.

Modified Randomized Study Population. The modified study population consists of all randomized patients who receive an ablation procedure, irrespective of whether the patient remains in the trial at the end of the blanking period.

Safety Population. The safety population consists of all randomized patients who receive an ablation procedure.

Modified Intent-to-Treat Population. The modified intent-to-treat population consists of all randomized patients who receive an ablation procedure and remain in follow-up at the close of the 90-day blanking period.

If the ablation procedure following randomization must be rescheduled, the rescheduled ablation procedure is still performed in accordance with the patient's randomized treatment assignment (MRI guided or PVI only) and will count as the time-0 for the blanking period and for the follow-up period so long as the ablation procedure is performed within 90 days of the pre-ablation MRI. If the ablation procedure is not performed within 90 days of the pre-ablation MRI the patient will be considered to be lost-to-follow-up and the patient will be excluded from each of the study populations defined above with the exception of the Randomized Study Population.

Unless indicated otherwise, all statistical analyses of efficacy outcomes will be performed in the modified intent-to-treat population and all analyses of safety outcomes will be carried out in the safety population.

4.2 Study Subjects

4.2.1 Inclusion and Exclusion Criteria

Inclusion criteria are:

1. Patients with persistent AF defined as 7 days or more of AF as evidenced by rhythm strips or written documentation; AND
2. Undergoing first AF ablation as per recent HRS consensus document 2 ; AND
3. Age \geq 18 years.

Patients are not eligible for DECAAF-II if they have any of the following exclusion criteria:

1. Previous left atrial ablation or any type of valvular surgery; OR
2. Contraindication for DE-MRI with a full dose of contrast agent; OR
3. Contraindication to beta blockers, if necessary, for DE-MRI; OR
4. Women currently pregnant; OR
5. Mental or physical inability to take part in the study; OR
6. Inability to be placed in MRI due to body mass or body habitus; OR
7. Known terminally ill patients; OR
8. Subjects without daily access to a smart phone or tablet compatible with the ECG Check application and ability to upload ECG tracings for the entire follow up period.

4.3 Sub-Populations

The key subgroups of interest in this trial are defined by subjects falling in Utah Stages I and II and those following into Utah Stages III and IV as determined by the pre-ablation MRI.

5 DATA REVIEW AND SUMMARY REPORTS

5.1 Data Review

5.2 Data Reports

5.3 Independent Review

6 GENERAL ANALYSIS ISSUES

6.1 Analysis software

Analysis will be performed using SAS® Software version 9.4 or later whenever possible. Other software packages, including R, STATA and StatXact®, may be used for particular specialized procedures.

6.2 Methods for withdrawals, missing data, and outliers

In accordance with the intent-to-treat principle all available data for subjects who are prematurely lost-to-follow-up will be retained in all analyses. It is expected that some patients may discontinue use of the ECG-check device prematurely, and that some of these patients may also fail to provide the end-of-study 12-lead ECG assessment stipulated in the protocol. However, these patients will continue to be monitored for repeat ablation or clinical AA recurrence until the patients' scheduled end of follow-up unless the patient is lost-to-follow-up. Accordingly, irrespective of the patient's adherence to the ECG-check schedule, subjects not achieving the primary outcome will be censored at the time of administrative censoring or loss-to-follow-up irrespective of adherence to the ECG-check.

Validity of the Kaplan-Meier estimates and logrank test assumes noninformative censoring, which is not formally testable. In the event that a substantial number of subjects are prematurely lost to follow-up, baseline characteristics, information from the 90-day MRI, and 30-day safety outcomes will be reviewed and compared to subjects not lost to follow up. If substantial discrepancies are detected between subjects who are prematurely lost to follow-up and those who are not prematurely lost, sensitivity analyses will be performed in which time-to-AA recurrence is compared between the randomized groups using inverse probability of censoring weights with probabilities of censoring estimated from variables measured at the baseline and month 3 assessments.

Because the analysis of the main secondary quality of life outcome based on the Toronto score will be performed using restricted likelihood-based estimation, the estimated treatment effects on the mean Toronto score will remain approximately unbiased so long as the pattern of missing data is consistent with a missing at random (MAR) mechanism. While the MAR assumption is not formally testable, if substantial discrepancies in baseline or follow-up characteristics are detected between patients with missing Toronto scores as compared to those with non-missing Toronto scores, sensitivity analyses will be performed in which the comparisons of the mean Toronto scores between the randomized groups is performed after adjustment for predicted probabilities of censoring estimated from variables measured at baseline and the 3-month follow-up assessment.

Outliers will be reviewed for validity. Outliers that are valid, for example, high laboratory values, will be included in all primary reports from this trial.

6.3 Multicenter Studies

The randomization sequences will be stratified by clinical center as well as dichotomized Utah Stage, to assure approximate balance of sites between the treatment arms at all times. The primary analysis will not incorporate stratification of covariate adjustment for center due to the relatively large number of centers included in the trial.

6.4 Multiple comparisons

As there is a single primary endpoint for this study, adjustment for multiple comparisons will not be required for the primary analysis. Similarly, multiple comparison adjustment is not required for the main secondary endpoint as a single main secondary comparison based on the Toronto score at 12 months has been defined.

Plans have not been developed for multiple comparison adjustment for analyses of other secondary outcomes. Hence, with the exception of consideration of stopping rules for repeated testing at multiple time points (see Section 7), and analyses of additional secondary endpoints will be performed on a comparison-wise basis, without formal adjustment for multiple comparisons in reports to the Data Safety and Monitoring Board. However, writing committees for specific manuscripts may define multiple comparison adjustments for secondary endpoints during the publications process. Reports from this trial should, whenever appropriate, note the nature of endpoints reported (primary vs. secondary) as well as relevant multiplicities of comparisons.

6.5 Derived and computed variables

All derived and computed variables will be outlined in the analysis dataset specifications for this study. These datasets are independently programmed by two statisticians. The SAS COMPARE procedure will be used to verify that the dual programmed analysis datasets are identical for each variable and each observation.

7 SCHEDULE OF PLANNED ANALYSES

7.1 Schedule of Interim Analyses

Interim analyses will be carried out after approximately 1/3 and after approximately 2/3 of the projected total number of events have occurred to guide the Data Safety and Monitoring Board in determining if the trial should be terminated early either due to clear evidence of a benefit of one of the treatment goals. Reports will include adverse events, unanticipated problems, and comparisons of primary and secondary outcomes between randomized groups for the full cohort and within the Utah Stages as described in Section 8.5. The α -spending function approach of Lan and DeMets will be applied under an approximate O'Brien-Fleming boundary to guide early termination due to efficacy. Conditional power calculations may be conducted at the request of the DSMB to evaluate futility; however the Steering Committee members have indicated that

they would prefer that the trial proceed to completion even in the absence of a trend for a treatment effect on the primary outcome.

Monitoring boundaries will be set according to the proportion of total statistical information available in each interim analysis dataset. Since this is an event based trial, this proportion will be the number of events recorded for the primary AA recurrence primary outcome divided by the required 517 total events which is documented in the sample size section of this document. Stopping boundaries will be generated using East statistical software. 2-sided symmetric monitoring boundaries will be used.

7.2 Efficacy Outcomes Evaluated in Interim Analyses

The primary outcome and each of the Category A secondary efficacy outcomes defined in Section 2 of the report will be compared between the randomized groups at each of the formal interim analyses using the methods described in Section 8 below. With the exception of the primary AA recurrence endpoint, which will be evaluated in accordance with the stopping boundary defined in Section 7.1 above, confidence intervals and p-values comparing other outcomes between randomized groups will be presented on a comparison-wise basis, without adjustment for multiple comparisons. DSMB reports at interim analyses will also contain descriptive summaries of Category B secondary efficacy outcomes.

7.3 Evaluation of Safety Outcomes

The primary safety composite and other safety outcomes designated in Section 8.4 below will also be compared between randomized groups at each interim analysis. Although the DSMB charter does not include a formal stopping guideline for safety, the results of the comparison of the primary safety composite between the randomized groups will be accompanied by the 2-sided Lan-DeMets stopping boundary corresponding to this outcome using an approximate Pocock boundary to assist the DSMB to interpret the results in the context of multiple interim analyses.

The frequencies of adverse cardiovascular and cerebrovascular events will be tabulated.

7.4 Subgroups in Interim Analyses

As described in Section 4.3 of this document, the two key subgroups of interest in this trial are defined by subjects falling in Utah Stages I and II and those following into Utah Stages III and IV as determined by the pre-ablation MRI. Key efficacy and safety results will be presented to the DSMB according to these subgroups as well as overall. If there is evidence of a Utah Stage-by-treatment interaction, the DSMB will have the option of examining subgroup-specific monitoring boundaries. Such boundaries, when presented to the DSMB, will be constructed to obtain an overall α of 0.025 across the 2 interim analyses and the final analysis to account for evaluation of two subgroups.

7.5 Blinding in the Interim Analysis

All interim analysis tables and analyses involving treatment arms will have treatment referred to as "Treatment A" and "Treatment B", consistently throughout the report presented to the DSMB.

As described in the DSMB charter, the DSMB will have the option of being unblinded to treatment arm identity at any time, by opening a sealed envelope containing these identities.

7.6 Schedule of Final Analyses

All final, planned analyses identified in the protocol and in this SAP will be performed only after all randomized patients have completed the protocol and the results of all significant queries have been resolved. Any post hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as such in all study publications.

8 PLANNED ANALYSES WITH PROCEDURES FOR COMPLETION

8.1 Analysis of Demographic and Other Pre-Treatment Characteristics

Descriptive summaries of baseline clinical and demographic characteristics will be provided by randomized treatment assignment for each analysis population. Baseline characteristics will also be summarized by randomized group in the modified intent-to-treat population for each geographic region (North America, Europe, and Asia). In the event that substantial imbalances in particular factors between the randomized treatment groups are detected, sensitivity analyses will be performed after adding these factors as stratification factors (for categorical baseline factors) or a covariates (for continuous baseline factors) to the Cox regression used for primary analysis of AA recurrence. Baseline characteristics will also be summarized by participate site without stratification by randomized group.

8.2 Analysis of Primary Outcome

The primary analysis will test the null hypothesis:

H_0 : The time between the completion of the 90 day blanking period and first AA recurrence has the same distribution for subjects assigned to the MRI-guided ablation as for subjects assigned to PVI-only ablation.

The alternative hypothesis is:

H_1 : The time between the completion of the 90 day blanking period and first AA recurrence has a different distribution for subjects assigned to the MRI-guided ablation as for subjects assigned to PVI-only ablation.

The primary efficacy analysis will be performed in the modified intent-to-treat population using a stratified log-rank test to compare the time to the first AA recurrence after the blanking period between the randomized treatment groups. Thus, time 0 for each subject will be the day following the completion of the blanking period, which is defined to occur 90 days following the ablation procedure. The log rank test will be stratified by Utah Stage (separate strata for Utah stages I - II, and III - IV). Follow-up will be censored at the administrative completion of the study, loss-to-follow-up or death. The primary analysis will be performed with a 2-sided significance level (α) of 0.05. The analysis will be carried out using SAS PROC LIFETEST.

An associated Cox proportional hazard regression analysis with the same stratification by Utah Stage will be performed to estimate the hazard ratio between the fibrosis guided ablation and conventional ablation groups with its 95% confidence interval. The analysis will be carried out using SAS PROC PHREG. The p-value for the effect of the treatment will be obtained using the score test.

In a sensitivity analyses the log rank test and associated Cox regression analyses will be repeated after considering any repeat ablations that occur during the blanking period as failures so that an AA recurrence is considered to have occurred on the first day of the follow-up period.

The possibility that the hazard ratio for treatment assignment varies over the follow-up period (non-proportional hazards) will be investigated by smoothed Schoenfeld residual plots and by performing time-dependent Cox regressions including interaction terms between treatment assignment and follow-up time.

Death will be censored as a competing risk in the primary analysis of AA recurrence. However, cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group using a competing risk framework. The cumulative incidence curves will be generated using the R package `cmprsk`.

8.3 Analysis of Secondary Outcomes

8.3.1 Components of AA Recurrence

The frequencies and proportions of patients experiencing each of three components of the primary AA outcome:

- atrial fibrillation
- atrial flutter
- atrial tachycardia

will be tabulated by treatment group. As in the primary analysis, only events occurring after the end of the blinding period will be counted in these analyses. Cox regression analyses in which the baseline hazard function is stratified by Utah stage will be used to obtain estimates of cause-specific hazard ratios and associated 95% confidence intervals to compare the three components of the primary outcome between the randomized treatment groups. Cumulative incidence curves will be constructed for each of the three components and death under the competing risk framework. Because these analyses of the components of the primary endpoint are explanatory, no adjustment for multiple comparisons will be performed.

8.3.2 Toronto Atrial Fibrillation Burden Scale

Quality of life as measured by the Toronto Atrial Fibrillation Burden Scale will be treated as the main secondary efficacy outcome. The main secondary analyses will estimate the effect of the treatment on the mean Toronto burden scores at months 3 and 12 under a linear mixed effects model in which the baseline Toronto burden score, visit month (treated as a categorical variable) and the interaction between treatment and visit month are included as fixed effects. The linear mixed effects analyses will be carried out using SAS PROC MIXED. An unstructured covariance model will be used to account for serial correlation in the Toronto scores across the follow-up visits. The main contrast for testing the effect of the treatment will compare the adjusted mean Toronto burden scores at month 12 between the guided ablation and usual care groups. A secondary contrast will compare the adjusted mean Toronto burden score at month 3 between the guided ablation and usual care groups. Additional contrasts will compare the average of the adjusted mean Toronto burden scores at months 3 and 12 and the change in the adjusted mean Toronto burden scores between months 3 and 12 between the randomized groups.

8.3.3 Additional Efficacy Outcomes

Time-to-event outcomes:

Stratified log-rank tests (stratified by Utah Stages I & II vs. III and IV) and associated Cox-regressions will also be used to compare initial occurrences of

- symptomatic AA recurrence,
- a composite outcome including AA recurrence and prescription of an anti-arrhythmic medication,
- a repeat ablation,
- first AA recurrence following repeat ablation,
- recurrence of arrhythmias other than AA

between the randomized treatment groups. The analysis of repeat ablations will evaluate the time from the end of the blanking period to the first ablation performed after the close of the blanking period. The analysis of AA recurrence following repeat ablation will evaluate the time from the end of the blanking period to the first AA recurrence following the first repeat ablation. If the patient has an AA recurrence after the blanking period but does not have a repeat ablation, the patient will be treated as censored without having had the event.

The following clinical events will be summarized by randomized treatment group:

- Cardiovascular (CV)-related hospitalization
- Stroke
- All-cause mortality
- Cardiovascular mortality.

In contrast to analyses of efficacy outcomes based on arrhythmia recurrence, analyses of these clinical events will be performed in the full Safety population, with time 0 defined as the date of the ablation procedure. Summaries for each clinical endpoint will include the number and proportion of patients experiencing at least one of the indicated events during the follow-up period as well as the rate of first events expressed per 100 patient-years of follow-up. Clinical event outcomes with at least 5 events within each of the randomized groups will be compared using log-rank tests and associated Cox regression analyses. However, because the expected numbers of events for these outcomes are relatively small, the baseline hazard functions will not be stratified by Utah Stage in these analyses.

Efficacy outcomes measured at scheduled visits:

Mixed effects analyses similar to those described for the Toronto score will be performed to compare the physical and mental health composite scores from the SF-36 between the randomized group at months 3 and 12. As for the Toronto score, primary emphasis will be given to the month-12 comparison, with secondary contrasts evaluating comparisons at month 3, the average of month 3 and month 12 and difference between month 12 and month 3 values. Similar analyses will also be performed for the 8 SF-36 domain subscales and for the Toronto AF Symptom score and the Toronto Health Care Utilization score.

The proportions of positive responses to the 5 questions asked every other week pertaining to chest pain, shortness of breath, heart racing, dizziness, and syncope will be

analyzed using weighted generalized estimating equations. A binary outcome model with logistic link function will be used for each of the 5 questions, with a working compound symmetry correlation matrix, with covariate adjustment for the baseline responses. The weights will be determined based on a missing data model which includes potential predictors of missingness as predictor variables. Contrasts will be defined to estimate odds ratios comparing the proportion of positive responses on each question between the two randomized groups at each visit a 2-week intervals across the follow-up periods, and to compare pooled estimates of proportions of positive responses over the 1-month blanking period, over successive 3-month intervals following the blanking period, and over the full follow-up period following the blanking period. The Huber sandwich estimator will be used to compute robust standard errors for statistical inferences. These analyses will be carried out using the SAS GENMOD procedure.

AA burden will be estimated for each month of follow-up for each subject as a time-weighted average of the proportion of ECG Check readings during that follow-up month which indicate the presence of AA. Generalized estimating equations using working compound symmetry correlation matrices with stabilized inverse probability of censoring weights to account for early loss-to-follow-up will be used to compare these proportions between the randomized treatment groups. The analysis will also be performed using SAS PROC GENMOD.

8.4 Analysis/Summary of Safety Outcomes

The primary safety composite outcome is defined by occurrence of one or more of the following events during the 30 day period following the ablation procedure:

- stroke
- pulmonary vein stenosis,
- bleeding requiring transfusion,
- heart failure and
- death.

Additional safety outcomes include each of the individual components of the primary safety composite as well as the occurrence of cardiac perforation or esophageal injury within 30 days of the ablation procedure. The primary safety composite and the other safety outcomes evaluated within 30 days of the ablation procedure will be summarized (with frequencies and % of randomized patients experiencing the endpoint provided for each randomized treatment group in the safety population) and will be compared between the randomized treatment groups using Fisher exact tests.

The above endpoints as well as all serious adverse events will also be monitored and documented throughout the follow-up period. Additionally, clinical sites will document all cardiovascular, cerebrovascular, and gastrointestinal adverse events (including non-serious adverse events in these categories) which are recorded in the patient record or reported at study visits.

Frequencies and proportions of the patients in the safety population experiencing each of the safety events (including the specific events indicated above as well as designated classes of SAEs) will be tabulated in the safety population by randomized group over the full follow-up period, including both the blanking period and the further follow-up after the close of the blanking period. Rates of the first occurrence of each type of event (expressed as the ratio of the number of patients with the event vs. the total number of patient-years of follow-up prior to censoring) will also be provided by randomized group.

The frequencies and proportions of patients experiencing each of the indicated safety events will also be provided separately for the following time periods during follow-up:

- a) The first 30 days after the ablation procedure,
- b) The first 90 days after the ablation procedure.

The total numbers of events corresponding to each safety endpoint (potentially including repeat events in the same patients), as well as associated rates expressed as the number of events per 100 patient-years of follow-up, will also be summarized over the full follow-up period, as well as for the first 30 days and the first 90 days after the ablation procedure.

8.5 Analysis of Subgroups

8.5.1 Subgroup Analyses of AA Recurrence

Stratified log-rank tests and Cox-regressions similar to those described for the primary analysis will be used to compare the fibrosis guided ablation and conventional interventions in subgroups defined by baseline fibrosis \leq or $>$ 20%. The log-rank test and Cox regression in the fibrosis \leq 20% subgroup will be stratified by Utah Stages I and II, while the analyses of the fibrosis $>$ 20% subgroup will be stratified by Utah Stages III and IV. These analyses will be repeated for the three components of the primary outcome. The p-value for the interaction between treatment and Utah Stage (I and II vs. III and IV) will be obtained by computing the z-score for the difference in the log hazard ratios between these baseline subgroups and comparing the z-score to the standard normal distribution.

The analyses described above relating randomized treatment assignment to the composite of AA recurrence and prescription of an anti-arrhythmic medication and to symptomatic AA recurrence will also be repeated for the Utah Stage I-II and Utah Stage III-IV groups, with interaction p-values computed as described above.

8.5.2 Analyses Relating AA Recurrence and Other Secondary Endpoints to Percent Fibrosis at Baseline

The objective of the analyses described in this section is to characterize the relationship of the percent fibrosis at baseline with the risk of AA recurrence and other designated secondary endpoints separately under the PVI alone intervention and under MRI guided fibrosis. Interest centers on the absolute risk of AA recurrence and the other designated secondary outcomes at different follow-up times and on the dose-response relationships between percent fibrosis and the hazard functions for the outcomes. We wish to characterize these dose-response relationships univariately, without covariate adjustment, and again after adjustment for baseline risk factors to characterize the extent to which percent fibrosis at baseline is independently predictive of AA recurrence and the other designated secondary outcomes.

8.5.2.1 Absolute risk of recurrence:

Cumulative incidence curves for the first AA recurrence and for death will be constructed under a competing risk framework by randomized group separately for each of the four Utah stages in order to estimate the proportions of subjects reaching these events by 6 months, 1 year and 18 months within each Utah stage.

8.5.2.2 Dose-response relationships between baseline % fibrosis and recurrence:

Separate Cox regression models using natural cubic splines for percent fibrosis will be used to relate the hazard for AA recurrence to the pre-ablation percent fibrosis within each randomized group. The cubic splines will be constructed with knot points at the 10th, 50th and 90th percentiles of the percent fibrosis distribution at baseline. This analysis will be repeated for the composite of AA recurrence and prescription of an anti-arrhythmic medication and to symptomatic AA recurrence. As for other Cox-regressions these analyses will evaluate the cause-specific hazards associated with the designated outcomes, with death censored as a competing risk.

The question of whether the dose-response relationships between percent fibrosis and the indicated outcomes differs between randomized groups will be addressed by fitting an extended Cox regression model in which the baseline hazard is stratified by randomized treatment assignment, and including pairwise interaction terms between the randomized groups and the natural cubic spline terms. A joint likelihood ratio test of equality of the Cox regression coefficients for all the cubic spline terms will be performed.

8.5.2.3 Analyses of percent residual fibrosis following ablation

The biological rationale for the trial is that MRI guided ablation will lead to greater coverage of fibrosis, and hence a reduced residual fibrosis following ablation, and that the reduced residual fibrosis will in turn reduce the risk of AA recurrence. Hence, analyses will be performed to describe the association of AA recurrence with residual fibrosis, quantified as the percent of the fibrotic portion of the atrial wall which is not covered by the ablation procedure. These analyses will also consider the success of encirclement of pulmonary veins, quantified as the number of the four pulmonary veins with uninterrupted scar encirclement. We note that the percent residual fibrosis and number of pulmonary veins encircled are determined by the results of the 90 day MRI in relation to the pre-ablation baseline MRI, while percent fibrosis is determined solely by the pre-ablation baseline MRI.

8.5.2.4 Relationship of percent residual fibrosis and number of pulmonary veins isolated with randomized treatment assignment

Univariate summary statistics, box plots, histograms, and overlaid kernel density curves will be used to display the distribution of percent residual fibrosis by randomized treatment group. These displays will be used to graphically display the overlap in the distributions of these parameters between the two randomized treatment groups. The number of pulmonary veins encircled will be tabulated by treatment group using frequency tables. The box plots and tabulation of number of pulmonary veins encircled will be provided overall, by region (US, China, Europe) and by clinical center.

Because percent residual fibrosis is expected to depend on both the pre-ablation percent fibrosis and the randomized treatment assignment, separate quantile regression analyses will

also be performed in each treatment group to depict the relationships between 20th, 50th, and 80th percentiles of percent residual fibrosis with the level of baseline percent fibrosis. The quantile regression curves will first be fit under a linear model and subsequently under a natural cubic spline model with knot points at the 10th, 50th and 90th percentiles, with a likelihood ratio test used to compare fits between models and select the optimum model. Graphical displays of the quantile regression curves overlaid for the two randomized treatment groups will be used to characterize the separation in percent residual fibrosis between randomized groups as a function of the percent fibrosis at baseline.

8.5.2.5 Relationship between AA recurrence and percent residual fibrosis, and number of pulmonary veins isolated

Cox regression analyses using natural cubic splines similar to those described for pre-ablation percent fibrosis will be used to relate AA recurrence to the percent of residual fibrosis within each randomized group. These analyses will be repeated for the composite of AA recurrence and prescription of an anti-arrhythmic medication and to symptomatic AA recurrence. Each of these analyses will be repeated after adding the number of pulmonary veins encircled to the model.

8.6 Analysis of Additional Exploratory Outcomes

8.6.1 Capability of Mobile Health Technology to Follow Patients After Ablation

The number of days with valid ECG Check readings will be tabulated weekly for each patient and summarized graphically by treatment group for each week throughout the follow-up period. The proportions of subjects with at least one valid ECG Check reading during each week of follow-up will be tabulated and graphically displayed. The largest gap (in days) between successive valid ECG Check recordings during the follow-up period will also be computed for each subject and summarized by randomized group.

DECAAF II SAP LAST VERSION

STATISTICAL ANALYSIS PLAN

Protocol Title: Efficacy of DE-MRI Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II)

Protocol Version and Date: 2.01; April 16, 2016

SAP Author:

SAP Version and Date: 2.0 SAP as of November 11, 2020

Amended at time of submission of the primary results manuscript to make the following corrections:

- 1) Name of the Toronto symptom severity scale corrected to state Symptom Severity Scale instead of Symptom Burden Scale.
- 2) The time period for the evaluation of the safety outcome is corrected to indicate 30 days after the ablation procedure, in accordance with the protocol, rather than 90 days.
- 3) Corrections to section and page numbers in table of contents
- 4) Protocol version number updated

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ABBREVIATIONS

ABBREVIATION	DEFINITION
CRF	Case Report Form
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
ITT	Intent-To-Treat Population
PP	Per-Protocol Population
FDA	United States Food and Drug Administration
SAP	Statistical Analysis Plan

1 PREFACE

1.1 Purpose of SAP

The Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the Protocol: Efficacy of DE-MRI Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II).

The SAP is important for the following reasons: (1) to ensure that data collected in the study are adequate to address the study hypotheses; (2) to prevent ad hoc decisions in analyzing study data; and (3) to prospectively identify a timeline and structure for completion of study analyses.

1.2 Auxiliary/Other Documents

The following documents were reviewed in preparation of this SAP

- Protocol: Efficacy of DE-MRI Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II)

1.3 SAP Version History

After a version of an analysis plan is approved for use in a study (for example, by a Data Safety Monitoring Board or study Principal Investigator), any subsequent changes to the SAP require a subsequent version of the SAP to be released. Each such subsequent version of a SAP must explicitly summarize all changes made in each SAP revision since the initially approved version. This section of the SAP contains that summary. All previous approved SAP versions must be archived and should be easily accessible for review if needed.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of the DECAAF II trial are:

1. to test the hypothesis that patients receiving fibrosis-guided ablation will have fewer AA recurrences than those who receive PVI ablation alone.
2. to test the hypothesis that receiving fibrosis-guided ablation will not be associated with increased rates of peri-procedural complications including stroke, pulmonary venous stenosis, bleeding, esophageal injury, cardiac perforation, heart failure, and death.

2.2 Study Endpoints

2.2.1 Primary Outcome

The primary endpoint is the recurrence of atrial arrhythmia post-ablation, defined as a non-self-terminating bout of atrial fibrillation, atrial flutter, or atrial tachycardia. The primary endpoint will be demonstrated by the occurrence of one of the following events during the study follow-up after the 90 blanking period:

- a) two consecutive, valid ECG tracings obtained between 6 hours and 7 days of each based on either the ECG Check model device, a 12-lead ECG, a 24 Holter or other continuous monitoring device,
- b) a repeat ablation.

It is expected that the majority of enrolled patients who reach the study outcome will do so due to two consecutive ECG Check tracings demonstrating AA as above. However, these same criteria, requiring demonstrated atrial arrhythmia occurrences no less than 6 hours and no more than 7 days apart, will also be applied to any readings obtained from 12-lead ECGs, Holter monitors, or other continuous recording devices. In some instances, this may mean that the study endpoint is achieved from a single monitoring study lasting more than 6 hours. It is also possible that a patient may achieve the study outcome from multiple sources (e.g., a single ECG Check reading of AA followed by a finding of AA from a 12-lead ECG performed 6 hours to 7 days later).

As described in Section 8.2, the primary analysis will compare the time from the completion of the 90-day blanking period to the subsequent occurrence of the primary endpoint between the randomized treatment groups. Any repeat ablations which occur during the 90 day blanking period will not be counted as events, and will not affect the definition of the start of the blanking period which is defined as the date of the initial post-randomization ablation.

2.2.2 Secondary Outcomes

The main secondary outcome is quality of life as assessed by the Toronto Atrial Fibrillation Symptom Severity Scale. The main secondary analyses will estimate the effect of the treatment on the mean Toronto Atrial Fibrillation Symptom Severity scores at months 3 and 12, with the 12-month comparison receiving primary emphasis in interpretation of the study results.

Additional secondary outcomes will be classified as Category A or Category B secondary outcomes, where outcomes in Category A will be subjected to more extensive statistical analyses than outcomes in Category B. The choice of which outcomes are placed in Categories A and B is based in part of their importance to the study and in part on technical considerations including statistical power, completeness of ascertainment, and measurement error. The designation of these two categories is not specified in the trial protocol, but rather is employed to simplify the description of the statistical analysis plan.

The Category A secondary efficacy outcomes are:

1. The composite of AA recurrence and prescription of an anti-arrhythmic medication
2. Symptomatic atrial arrhythmia
3. Repeat ablation
4. Stroke
5. Cardiovascular (CV)-related hospitalization
6. The RAND SF-36 physical and mental health summary scores obtained at month 3 and month 12,
7. The AF Symptom scores obtained at month 3 and month 12 during follow-up.

The individual components of the primary outcome are:

- atrial fibrillation
- atrial flutter
- atrial tachycardia

will also be evaluated as Category A secondary outcomes.

The statistical analyses of the composite of AA recurrence and prescription of an anti-arrhythmic medication, symptomatic atrial arrhythmia, repeat ablation, and the individual components of the primary outcome will compare the time from completion of the 90-day blanking period to the first occurrence of the indicated events during the subsequent study follow-up between the randomized groups. The statistical analyses of the stroke and CV-hospitalization endpoints will compare the time from the initial ablation procedure to the occurrence of these endpoints at any time during follow-up, including the blanking period. See Section 8.3 for additional details.

The Category B secondary outcomes include:

1. Cardiovascular mortality
2. AA recurrence following repeat ablation
3. Arrhythmias other than AA

4. AA burden, determined for each month of follow-up as the proportion of ECG Check readings during that follow-up month which indicate the presence of AA.

5. The 8 individual SF-36 health subscales: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perception assessed at 3 months and 12 months follow-up the initial ablation procedure.

As with the primary endpoint, arrhythmias other than AA must be confirmed by 2-consecutive valid ECG tracings obtained either by the ECG Check model device, a 12-lead ECG, or a 24-hour Holter or alternative continuous monitoring device. Analyses of cardiovascular mortality will include all cardiovascular deaths during the follow-up period following the initial ablation procedure. Analyses of AA recurrence following repeat ablation and AA burden will be defined using AA-recurrence information during the follow-up subsequent to the 90 day blanking period.

2.2.3 Safety Outcomes

The main safety outcome is a composite endpoint defined by occurrence of any of the following events within 30 days of the ablation procedure:

- stroke
- pulmonary vein stenosis,
- bleeding requiring transfusion,
- heart failure and
- death.

Additional safety outcomes include:

- Each of the individual components of the primary safety composite
- Cardiac perforation within 30 days of the ablation procedure
- Esophageal injury within 30 days of the ablation procedure

SAEs which occur at any time during the follow-up period of the trial will be tabulated in accordance with standard MEDRA classifications.

2.3 Covariates

Because this is a randomized trial, covariate adjustment for baseline characteristics is not necessary to provide unbiased estimates of treatment effect. However, the primary analysis will be stratified by Utah Stage (Utah stage categories I & II vs. categories III & IV), and a number of the secondary analyses will relate study outcomes to Utah stage or the % fibrosis at baseline, which is the continuous measure used to define Utah stage.

3 STUDY DESIGN AND METHODS

3.1 Overall Study Design

DECAAF II is a prospective, randomized, multi-center trial of patients with persistent AF and presence of atrial fibrosis. Subjects will be randomized to one of two study groups to receive conventional PVI ablation (Group 1) or PVI + fibrosis-guided ablation (Group 2). Details of the two treatments can be found in the Protocol.

3.2 Randomization and Blinding

3.2.1 Randomization

Randomization to each treatment will be in a 1:1 ratio stratified by Utah stage (I-II vs III-IV) and clinical center. Randomized permuted blocks will be used for randomization. This trial will use a web-based system for randomization.

After consenting to participate in the study, the subject will undergo a DE-MRI scan to assess for extent of atrial fibrosis. After the DCC has verified adequate quality of the DE-MRI, study subjects will be randomized to receive PVI alone or fibrosis-guided ablation. The DCC will complete randomization and notify the site no more than 96 hours before the scheduled procedure to allow adequate time for scheduling and preparation.

3.2.2 Blinding

The ablationists for patients randomized to the PVI ablation group will be kept blinded to the pre-ablation MRI fibrosis results. In addition, MRI image processors will be blinded to arm assignment and all readings of the ECG data used to determine the primary outcome will be blinded to the patient's randomized treatment arm. The site PI and staff may be aware of the patient's randomized treatment assignment, but will be instructed to limit the number of individuals aware of the patient's randomized assignment to the extent possible. All reasonable efforts will be made to keep the patient blinded to their randomized treatment assignment.

3.3 Sample Size and Power Determination

The original protocol stipulated that using an event-driven design, the trial will proceed until a total of approximately 517 arrhythmia recurrence events are recorded to provide 90% power with a 2-sided Type 1 error of 0.05 to detect a reduction in the hazard rate for arrhythmia recurrence by 25% in the fibrosis guided ablation group compared to the conventional ablation group. A total sample size of 888 randomized patients is estimated to provide the required 517 events under the following assumptions:

- 60% of conventional ablation subjects have AA recurrence by 1 year after ablation (9 months after the end of the blanking period), and 68% have AA recurrence by 18 months after ablation; and

- the hypothesized relative reduction in the AA recurrence event rate is 25% in the fibrosis-guided ablation group compared to the conventional ablation group; and
- 3% of subjects are lost during the 90 day blanking period, and 0.45% of subjects subsequently die or are lost to follow-up per month; and
- patients are accrued uniformly over a 12-month accrual period; and
- follow-up will extend for 18 months following each patient's ablation procedure or until a common administrative censoring date 12 months after the ablation procedure of the final randomized subject, whichever comes first; and
- two interim analyses are performed after approximately 1/3 and 2/3 of the total projected number of events have been observed using an O'Brien-Fleming type stopping boundary.

The original protocol also stipulated that interim assessments of the actual accrual and event rate (blinded to treatment assignment) will be used to modify the actual number of randomized patients above or below 888 patients in order to give high confidence that at least 517 AA recurrence events are observed. The projected number of required patients would be 744 if the AA recurrence percentage is 70% at 1 year and 1061 if the AA recurrence percentage is 50% at 1 year. It is possible that the accrual period may extend more than 12 months; if this occurs the average follow-up time will be increased as a greater proportion of patients would be enrolled at least 18 months prior to the common administrative censoring date for the trial, and the required number of patients may be slightly reduced.

Various approaches, including projections and simulations based on study data observed to date, may be implemented to estimate numbers of events expected in the study population under scenarios where recruitment is stopped at a certain number of patients. Such approaches should again give high confidence (e.g. 95% or greater) that the required number of events will be achieved under realistic study scenarios.

During the conduct of the trial, it became apparent that the event rate was going to be less than projected but that it was not financially or logistically feasible to extend enrollment sufficiently to achieve the originally targeted 517 AA recurrence events for the primary outcome. Accordingly, in January 2020 the target sample size was reduced to 900 patients, and the end of enrollment was designated to occur on January 31, 2020. Based on an observed event rate in the trial at the time of 40%, the projected 900 randomized patients were projected to provide 360 AA recurrence events. Ultimately, a total of 842 patients were randomized, and the projected event rate (based on the study data as of the January, 2020) was increased to 43%, leading to a projected 362 events for the primary AA recurrence outcome. This number of events was projected to provide 80% power with 2-sided $\alpha=0.05$ to detect a hazard ratio of 0.74 (corresponding to a 26% hazard reduction) for the fibrosis guided ablation group compared to the control group, and 90% power to detect a hazard ratio of 0.71 (corresponding to a 29% hazard reduction).

4 STUDY SUBJECTS AND ANALYSIS POPULATIONS

4.1 Analysis Population

Randomized Study Population. The randomized study population consists of all randomized patients, irrespective of whether the patient receives an ablation procedure or remains in the trial at the close of the blanking period.

Modified Randomized Study Population. The modified study population consists of all randomized patients who receive an ablation procedure, irrespective of whether the patient remains in the trial at the end of the blanking period.

Safety Population. The safety population consists of all randomized patients who receive an ablation procedure. The safety population is the same as the modified randomized study population.

Modified Intent-to-Treat Population. The modified intent-to-treat population consists of all randomized patients who receive an ablation procedure and remain in follow-up at the close of the 90-day blanking period.

If the ablation procedure following randomization must be rescheduled, the rescheduled ablation procedure is still performed in accordance with the patient's randomized treatment assignment (MRI guided or PVI only) and will count as the time-0 for the blanking period and for the follow-up period so long as the ablation procedure is performed within 90 days of the pre-ablation MRI. If the ablation procedure is not performed within 90 days of the pre-ablation MRI the patient will be considered to be lost-to-follow-up and the patient will be excluded from each of the study populations defined above with the exception of the Randomized Study Population.

Unless indicated otherwise, all statistical analyses of efficacy outcomes will be performed in the modified intent-to-treat population and all analyses of safety outcomes will be carried out in the safety population.

4.2 Study Subjects

4.2.1 Inclusion and Exclusion Criteria

Inclusion criteria are:

1. Patients with persistent AF defined as 7 days or more of AF as evidenced by rhythm strips or written documentation; AND
2. Undergoing first AF ablation as per recent HRS consensus document 2 ; AND
3. Age \geq 18 years.

Patients are not eligible for DECAAF-II if they have any of the following exclusion criteria:

1. Previous left atrial ablation or any type of valvular surgery; OR
2. Contraindication for DE-MRI with a full dose of contrast agent; OR
3. Contraindication to beta blockers, if necessary, for DE-MRI; OR
4. Women currently pregnant; OR
5. Mental or physical inability to take part in the study; OR
6. Inability to be placed in MRI due to body mass or body habitus; OR
7. Known terminally ill patients; OR

8. Subjects without daily access to a smart phone or tablet compatible with the ECG Check application and ability to upload ECG tracings for the entire follow up period.

4.3 Sub-Populations

The key subgroups of interest in this trial are defined by subjects falling in Utah Stages I and II and those following into Utah Stages III and IV as determined by the pre-ablation MRI.

5 GENERAL ANALYSIS ISSUES

5.1 Analysis software

Analysis will be performed using SAS® Software version 9.4 or later whenever possible. Other software packages, including R, STATA and StatXact®, may be used for particular specialized procedures.

5.2 Methods for withdrawals, missing data, and outliers

In accordance with the intent-to-treat principle all available data for subjects who are prematurely lost-to-follow-up will be retained in all analyses. It is expected that some patients may discontinue use of the ECG-check device prematurely, and that some of these patients may also fail to provide the end-of-study 12-lead ECG assessment stipulated in the protocol. However, these patients will continue to be monitored for repeat ablation or clinical AA recurrence until the patients' scheduled end of follow-up unless the patient is lost-to-follow-up. Accordingly, irrespective of the patient's adherence to the ECG-check schedule, subjects not achieving the primary outcome will be censored at the time of administrative censoring or loss-to-follow-up irrespective of adherence to the ECG-check.

Validity of the Kaplan-Meier estimates and logrank test assumes noninformative censoring, which is not formally testable. In the event that a substantial number of subjects are prematurely lost to follow-up, baseline characteristics, information from the 90-day MRI, and 30-day safety outcomes will be reviewed and compared to subjects not lost to follow up. If substantial discrepancies are detected between subjects who are prematurely lost to follow-up and those who are not prematurely lost, sensitivity analyses will be performed in which time-to-AA recurrence is compared between the randomized groups using inverse probability of censoring weights with probabilities of censoring estimated from variables measured at the baseline and month 3 assessments.

Because the analysis of the main secondary quality of life outcome based on the Toronto symptom severity score will be performed using restricted likelihood-based estimation, the estimated treatment effects on the mean Toronto symptom severity score will remain approximately unbiased so long as the pattern of missing data is consistent with a missing at random (MAR) mechanism. While the MAR assumption is not formally testable, if substantial discrepancies in baseline or follow-up characteristics are detected between patients with missing Toronto symptom severity scores as compared to those with non-missing Toronto symptom severity scores, sensitivity analyses will be performed in which the comparisons of the mean Toronto symptom severity scores between the randomized groups is performed after adjustment for predicted probabilities of censoring estimated from variables measured at baseline and the 3-month follow-up assessment.

Outliers will be reviewed for validity. Outliers that are valid, for example, high laboratory values, will be included in all primary reports from this trial.

5.3 Multicenter Studies

The randomization sequences will be stratified by clinical center as well as dichotomized Utah Stage, to assure approximate balance of sites between the treatment arms at all times. The primary analysis will not incorporate stratification of covariate adjustment for center due to the relatively large number of centers included in the trial.

5.4 Multiple comparisons

As there is a single primary endpoint for this study, adjustment for multiple comparisons will not be required for the primary analysis. Similarly, multiple comparison adjustment is not required for the main secondary endpoint as a single main secondary comparison based on the Toronto symptom severity score at 12 months has been defined.

Plans have not been developed for multiple comparison adjustment for analyses of other secondary outcomes. Hence, with the exception of consideration of stopping rules for repeated testing at multiple time points (see Section 7), and analyses of additional secondary endpoints will be performed on a comparison-wise basis, without formal adjustment for multiple comparisons in reports to the Data Safety and Monitoring Board. However, writing committees for specific manuscripts may define multiple comparison adjustments for secondary endpoints during the publications process. Reports from this trial should, whenever appropriate, note the nature of endpoints reported (primary vs. secondary) as well as relevant multiplicities of comparisons.

5.5 Derived and computed variables

All derived and computed variables will be outlined in the analysis dataset specifications for this study. These datasets are independently programmed by two statisticians. The SAS COMPARE procedure will be used to verify that the dual programmed analysis datasets are identical for each variable and each observation.

6 SCHEDULE OF PLANNED ANALYSES

6.1 Schedule of Interim Analyses

The initial study protocol stipulated that Interim analyses would be carried out after approximately 1/3 and after approximately 2/3 of the projected total number of events have occurred to guide the Data Safety and Monitoring Board in determining if the trial should be terminated early either due to clear evidence of a benefit of one of the treatment goals. Reports will include adverse events, unanticipated problems, and comparisons of primary and secondary outcomes between randomized groups for the full cohort and within the Utah Stages as described in Section 8.5. The α -spending function approach of Lan and DeMets will be applied under an approximate O'Brien-Fleming boundary to guide early termination due to efficacy. Conditional power calculations may be conducted at the request of the DSMB to evaluate futility; however the Steering Committee members have indicated that they would prefer that the trial proceed to completion even in the absence of a trend for a treatment effect on the primary outcome.

Monitoring boundaries will be set according to the proportion of total statistical information available in each interim analysis dataset. Since this is an event based trial, this proportion will be the number of events recorded for the primary AA recurrence primary outcome divided by the required 517 total events which is documented in the sample size section of this document. Stopping boundaries will be generated using appropriate statistical software. 2-sided symmetric monitoring boundaries will be used.

During study conduct, the initial interim analysis was conducted in accordance with the formal stopping rule described below as planned. However, as it became clear that the targeted 517 primary outcome events could not be achieved, subsequent interim analyses were performed for evaluation of safety only, without formal consideration for early stopping due to safety.

6.2 Efficacy Outcomes Evaluated in Interim Analyses

The primary outcome and each of the Category A secondary efficacy outcomes defined in Section 2 of the report will be compared between the randomized groups at each of the formal interim analyses using the methods described in Section 8 below. With the exception of the primary AA recurrence endpoint, which will be evaluated in accordance with the stopping boundary defined in Section 7.1 above, confidence intervals and p-values comparing other outcomes between randomized groups will be presented on a comparison-wise basis, without adjustment for multiple comparisons. DSMB reports at interim analyses will also contain descriptive summaries of Category B secondary efficacy outcomes.

6.3 Evaluation of Safety Outcomes

The primary safety composite and other safety outcomes designated in Section 8.4 below will also be compared between randomized groups at each interim analysis. Although the DSMB charter does not include a formal stopping guideline for safety, the results of the comparison of the primary safety composite between the randomized groups will be accompanied by the 2-sided Lan-DeMets stopping boundary corresponding to this outcome using an approximate

Pockcock boundary to assist the DSMB to interpret the results in the context of multiple interim analyses.

The frequencies of adverse cardiovascular and cerebrovascular events will be tabulated.

6.4 Subgroups in Interim Analyses

As described in Section 4.3 of this document, the two key subgroups of interest in this trial are defined by subjects falling in Utah Stages I and II and those following into Utah Stages III and IV as determined by the pre-ablation MRI. Key efficacy and safety results will be presented to the DSMB according to these subgroups as well as overall. If there is evidence of a Utah Stage-by-treatment interaction, the DSMB will have the option of examining subgroup-specific monitoring boundaries. Such boundaries, when presented to the DSMB, will be constructed to obtain an overall α of 0.025 across the 2 interim analyses and the final analysis to account for evaluation of two subgroups.

6.5 Blinding in the Interim Analysis

All interim analysis tables and analyses involving treatment arms will have treatment referred to as "Treatment A" and "Treatment B", consistently throughout the report presented to the DSMB. As described in the DSMB charter, the DSMB will have the option of being unblinded to treatment arm identity at any time, by opening a sealed envelope containing these identities.

6.6 Schedule of Final Analyses

All final, planned analyses identified in the protocol and in this SAP will be performed only after all randomized patients have completed the protocol and the results of all significant queries have been resolved. Any post hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as such in all study publications.

7 PLANNED ANALYSES WITH PROCEDURES FOR COMPLETION

7.1 Analysis of Demographic and Other Pre-Treatment Characteristics

Descriptive summaries of baseline clinical and demographic characteristics will be provided by randomized treatment assignment for each analysis population. Baseline characteristics will also be summarized by randomized group in the modified intent-to-treat population for each geographic region (North America, Europe, and Asia). In the event that substantial imbalances in particular factors between the randomized treatment groups are detected, sensitivity analyses will be performed after adding these factors as stratification factors (for categorical baseline factors) or a covariates to the Cox regression used for primary analysis of AA recurrence. Baseline characteristics will also be summarized by participate site without stratification by randomized group.

7.2 Analysis of Primary Outcome

The primary analysis will test the null hypothesis:

H_0 : The time between the completion of the 90 day blanking period and first AA recurrence has the same distribution for subjects assigned to the MRI-guided ablation as for subjects assigned to PVI-only ablation.

The alternative hypothesis is:

H_1 : The time between the completion of the 90 day blanking period and first AA recurrence has a different distribution for subjects assigned to the MRI-guided ablation as for subjects assigned to PVI-only ablation.

The primary efficacy analysis will be performed in the modified intent-to-treat population using a stratified log-rank test to compare the time to the first AA recurrence after the blanking period between the randomized treatment groups. Thus, time 0 for each subject will be the day following the completion of the blanking period, which is defined to occur 90 days following the ablation procedure. The log rank test will be stratified by Utah Stage (separate strata for Utah stages I - II, and III - IV). Follow-up will be censored at the administrative completion of the study, loss-to-follow-up or death. The primary analysis will be performed with a 2-sided significance level (α) of 0.05. The analysis will be carried out using SAS PROC LIFETEST.

An associated Cox proportional hazard regression analysis with the same stratification by Utah Stage will be performed to estimate the hazard ratio between the fibrosis guided ablation and conventional ablation groups with its 95% confidence interval. The analysis will be carried out using SAS PROC PHREG. The p-value for the effect of the treatment will be obtained using the score test.

In a sensitivity analyses the log rank test and associated Cox regression analyses will be repeated after considering any repeat ablations that occur during the blanking period as failures so that an AA recurrence is considered to have occurred on the first day of the follow-up period.

The possibility that the hazard ratio for treatment assignment varies over the follow-up period (non-proportional hazards) will be investigated by smoothed Schoenfeld residual plots and by performing time-dependent Cox regressions including interaction terms between treatment assignment and follow-up time. Death will be censored as a competing risk in the

primary analysis of AA recurrence. However, cumulative incidence curves for the first AA recurrence and for death will be constructed by randomized group using a competing risk framework. The cumulative incidence curves will be generated using the R package *cmprsk*.

7.3 Analysis of Secondary Outcomes

7.3.1 Components of AA Recurrence

The frequencies and proportions of patients experiencing each of three components of the primary AA outcome:

- atrial fibrillation
- atrial flutter
- atrial tachycardia

will be tabulated by treatment group. As in the primary analysis, only events occurring after the end of the blanking period will be counted in these analyses. Cox regression analyses in which the baseline hazard function is stratified by Utah stage will be used to obtain estimates of cause-specific hazard ratios and associated 95% confidence intervals to compare the three components of the primary outcome between the randomized treatment groups. Cumulative incidence curves will be constructed for each of the three components and death under the competing risk framework. Because these analyses of the components of the primary endpoint are explanatory, no adjustment for multiple comparisons will be performed.

7.3.2 Toronto Atrial Fibrillation Severity Scale

Quality of life as measured by the Toronto Atrial Fibrillation Symptom Severity Scale will be treated as the main secondary efficacy outcome. The main secondary analyses will estimate the effect of the treatment on the mean Toronto symptom severity scores at months 3 and 12 under a linear mixed effects model in which the baseline Toronto symptom severity score, visit month (treated as a categorical variable) and the interaction between treatment and visit month are included as fixed effects. The linear mixed effects analyses will be carried out using SAS PROC MIXED. An unstructured covariance model will be used to account for serial correlation in the Toronto symptom severity scores across the follow-up visits. The main contrast for testing the effect of the treatment will compare the adjusted mean Toronto symptom severity scores at month 12 between the guided ablation and usual care groups. A secondary contrast will compare the adjusted mean Toronto symptom severity score at month 3 between the guided ablation and usual care groups. Additional contrasts will compare the average of the adjusted mean Toronto severity scores at months 3 and 12 and the change in the adjusted mean Toronto symptom severity scores between months 3 and 12 between the randomized groups.

7.3.3 Additional Efficacy Outcomes

Time-to-event outcomes:

Stratified log-rank tests (stratified by Utah Stages I & II vs. III and IV) and associated Cox-regressions will also be used to compare initial occurrences of

- symptomatic AA recurrence,
- a composite outcome including AA recurrence and prescription of an anti-arrhythmic medication,
- a repeat ablation,
- first AA recurrence following repeat ablation,
- recurrence of arrhythmias other than AA

between the randomized treatment groups. The analysis of repeat ablations will evaluate the time from the end of the blanking period to the first ablation performed after the close of the blanking period. The analysis of AA recurrence following repeat ablation will evaluate the time from the end of the blanking period to the first AA recurrence following the first repeat ablation. If the patient has an AA recurrence after the blanking period but does not have a repeat ablation, the patient will be treated as censored without having had the event.

The following clinical events will be summarized by randomized treatment group:

- Cardiovascular (CV)-related hospitalization
- Stroke
- All-cause mortality
- Cardiovascular mortality.

In contrast to analyses of efficacy outcomes based on arrhythmia recurrence, analyses of these clinical events will be performed in the full Safety population, with time 0 defined as the date of the ablation procedure. Summaries for each clinical endpoint will include the number and proportion of patients experiencing at least one of the indicated events during the follow-up period as well as the rate of first events expressed per 100 patient-years of follow-up. Clinical event outcomes with at least 5 events within each of the randomized groups will be compared using log-rank tests and associated Cox regression analyses. However, because the expected numbers of events for these outcomes are relatively small, the baseline hazard functions will not be stratified by Utah Stage in these analyses.

Efficacy outcomes measured at scheduled visits:

Mixed effects analyses similar to those described for the Toronto symptom severity score will be performed to compare the physical and mental health composite scores from the SF-36 between the randomized group at months 3 and 12. As for the Toronto score, primary emphasis will be given to the month-12 comparison, with secondary contrasts evaluating comparisons at month 3, the average of month 3 and month 12 and difference between month 12 and month 3 values. Similar analyses will also be performed for the 8 SF-36 domain subscales and for the Toronto global health score.

AA burden will be estimated for each month of follow-up for each subject as a time-weighted average of the proportion of ECG Check readings during that follow-up month which indicate the presence of AA. Generalized estimating equations using working compound symmetry correlation matrices with stabilized inverse probability of censoring weights to account for early loss-to-follow-up will be used to compare these proportions between the randomized treatment groups. The analysis will also be performed using SAS PROC GENMOD.

7.4 Analysis/Summary of Safety Outcomes

The primary safety composite outcome is defined by occurrence of one or more of the following events during the 30 day period following the ablation procedure:

- stroke
- pulmonary vein stenosis,
- bleeding requiring transfusion,
- heart failure and
- death.

Additional safety outcomes include each of the individual components of the primary safety composite as well as the occurrence of cardiac perforation or esophageal injury within 30 days of the ablation procedure. The primary safety composite and the other safety outcomes evaluated within 30 days of the ablation procedure will be summarized (with frequencies and % of randomized patients experiencing the endpoint provided for each randomized treatment group in the safety population) and will be compared between the randomized treatment groups using Fisher exact tests.

The above endpoints as well as all serious adverse events will also be monitored and documented throughout the follow-up period. Additionally, clinical sites will document all cardiovascular, cerebrovascular, and gastrointestinal adverse events (including non-serious adverse events in these categories) which are recorded in the patient record or reported at study visits.

Frequencies and proportions of the patients in the safety population experiencing each of the safety events (including the specific events indicated above as well as designated classes of SAEs) will be tabulated in the safety population by randomized group over the full follow-up period, including both the blanking period and the further follow-up after the close of the blanking period. Rates of the first occurrence of each type of event (expressed as the ratio of the number of patients with the event vs. the total number of patient-years of follow-up prior to censoring) will also be provided by randomized group.

The frequencies and proportions of patients experiencing each of the indicated safety events will also be provided separately for the following time period during follow-up:

- a) The first 30 days after the ablation procedure.

The total numbers of events corresponding to each safety endpoint (potentially including repeat events in the same patients), as well as associated rates expressed as the number of events per 100 patient-years of follow-up, will also be summarized over the full follow-up period, as well as for the first 30 days after the ablation procedure.

7.5 Analysis of Subgroups

7.5.1 Subgroup Analyses of AA Recurrence

Stratified log-rank tests and Cox-regressions similar to those described for the primary analysis will be used to compare the fibrosis guided ablation and conventional interventions in subgroups defined by baseline fibrosis \leq or $>$ 20%. The log-rank test and Cox regression in the fibrosis \leq 20% subgroup will be stratified by Utah Stages I and II, while the analyses of the fibrosis $>$ 20% subgroup will be stratified by Utah Stages III and IV. These analyses will be repeated for the three components of the primary outcome. The p-value for the interaction between treatment and Utah Stage (I and II vs. III and IV) will be obtained by computing the z-score for the

difference in the log hazard ratios between these baseline subgroups and comparing the z-score to the standard normal distribution.

The analyses described above relating randomized treatment assignment to the composite of AA recurrence and prescription of an anti-arrhythmic medication and to symptomatic AA recurrence will also be repeated for the Utah Stage I-II and Utah Stage III-IV groups, with interaction p-values computed as described above.

7.5.2 Analyses Relating AA Recurrence and Other Secondary Endpoints to Percent Fibrosis at Baseline

The objective of the analyses described in this section is to characterize the relationship of the percent fibrosis at baseline with the risk of AA recurrence and other designated secondary endpoints separately under the PVI alone intervention and under MRI guided fibrosis. Interest centers on the absolute risk of AA recurrence and the other designated secondary outcomes at different follow-up times and on the dose-response relationships between percent fibrosis and the hazard functions for the outcomes. We wish to characterize these dose-response relationships univariately, without covariate adjustment, and again after adjustment for baseline risk factors to characterize the extent to which percent fibrosis at baseline is independently predictive of AA recurrence and the other designated secondary outcomes.

7.5.2.1 Absolute risk of recurrence:

Cumulative incidence curves for the first AA recurrence and for death will be constructed under a competing risk framework by randomized group separately for each of the four Utah stages in order to estimate the proportions of subjects reaching these events by 6 months, 1 year and 18 months within each Utah stage.

7.5.2.2 Dose-response relationships between baseline % fibrosis and recurrence:

Separate Cox regression models using natural cubic splines for percent fibrosis will be used to relate the hazard for AA recurrence to the pre-ablation percent fibrosis within each randomized group. The natural cubic splines will be constructed with knot points at the 10th, 50th and 90th percentiles of the percent fibrosis distribution at baseline. This analysis will be repeated for the composite of AA recurrence and prescription of an anti-arrhythmic medication and to symptomatic AA recurrence. As for other Cox-regressions these analyses will evaluate the cause-specific hazards associated with the designated outcomes, with death censored as a competing risk. In order to assess if the cubic spline model with 3 knot points provides a sufficiently good fit to the true dose response relationships between pre-ablation percent fibrosis and the hazard for AA recurrence we will also fit cubic spline models with additional knot points. If the Bayes Information Criteria and visual inspection of the fitted curves suggests additional knot points are required, we will fit curves with additional knot points in place of the curves with 3 knot points.

The question of whether the dose-response relationships between percent fibrosis and the indicated outcomes differs between randomized groups will be addressed by fitting an extended

Cox regression model with main effects for the randomized treatment group and the cubic spline terms in pre-ablation percent fibrosis as well as a pairwise interaction term between the randomized groups and the natural cubic spline terms. A joint likelihood ratio test of equality of the Cox regression coefficients for all the cubic spline terms will be performed. We will also use this model to display the estimated hazard ratio comparing AA recurrence between the fibrosis guided and PVI only groups as a function of percent fibrosis with a 95% pointwise confidence band.

7.5.2.3 Analyses of percent residual fibrosis following ablation

The biological rationale for the trial is that MRI guided ablation will lead to greater coverage of fibrosis, and hence a reduced residual fibrosis following ablation, and that the reduced residual fibrosis will in turn reduce the risk of AA recurrence. Hence, analyses will be performed to describe the association of AA recurrence with residual fibrosis, quantified as the percent of the fibrotic portion of the atrial wall which is not covered by the ablation procedure. These analyses will also consider the success of encirclement of pulmonary veins, quantified as the number of the four pulmonary veins with uninterrupted scar encirclement. We note that the percent residual fibrosis and number of pulmonary veins encircled are determined by the results of the 90 day MRI in relation to the pre-ablation baseline MRI, while percent fibrosis is determined solely by the pre-ablation baseline MRI.

7.5.2.4 Relationship of percent residual fibrosis and number of pulmonary veins isolated with randomized treatment assignment

Univariate summary statistics, box plots, histograms, and overlaid kernel density curves will be used to display the distribution of percent residual fibrosis by randomized treatment group. These displays will be used to graphically display the overlap in the distributions of these parameters between the two randomized treatment groups. The number of pulmonary veins encircled will be tabulated by treatment group using frequency tables. The box plots and tabulation of number of pulmonary veins encircled will be provided overall, by region (US, China, Europe) and by clinical center.

Because percent residual fibrosis is expected to depend on both the pre-ablation percent fibrosis and the randomized treatment assignment, separate quantile regression analyses will also be performed in each treatment group to depict the relationships between 20th, 50th, and 80th percentiles of percent residual fibrosis with the level of baseline percent fibrosis. The quantile regression curves will first be fit under a linear model and subsequently under a natural cubic spline model with knot points at the 10th, 50th and 90th percentiles, with a likelihood ratio test used to compare fits between models and select the optimum model. Graphical displays of the quantile regression curves overlaid for the two randomized treatment groups will be used to characterize the separation in percent residual fibrosis between randomized groups as a function of the percent fibrosis at baseline.

7.5.2.5 Relationship between AA recurrence and percent residual fibrosis, and number of pulmonary veins isolated

Cox regression analyses using natural cubic splines similar to those described for pre-ablation percent fibrosis will be used to relate AA recurrence to the percent of residual fibrosis within

each randomized group. These analyses will be repeated for the composite of AA recurrence and prescription of an anti-arrhythmic medication and to symptomatic AA recurrence. Each of these analyses will be repeated after adding the number of pulmonary veins encircled to the model.

7.6 Analysis of Additional Exploratory Outcomes

7.6.1 Capability of Mobile Health Technology to Follow Patients After Ablation

The number of days with valid ECG Check readings will be tabulated weekly for each patient and summarized graphically by treatment group for each week throughout the follow-up period. The proportions of subjects with at least one valid ECG Check reading during each week of follow-up will be tabulated and graphically displayed. The largest gap (in days) between successive valid ECG Check recordings during the follow-up period will also be computed for each subject and summarized by randomized group.

Background to Analyses and Corrections to SAP

We have attached the final SAP for the DECAAF II Trial which was saved on 1/21/2021.

Some analyses described in the SAP, particularly those involving the quality of life instruments and long-term cardiovascular and cerebrovascular events, have been designated for subsequent publications. Conversely, certain as-treated analyses based on the 5-level ordinal scales for targeted and covered fibrosis, which had originally been planned for the study's second publication and which are not included in the SAP, have been included in the primary manuscript. The analyses of the current submission incorporated the following four addendums to the SAP of 1/21/2021:

- 1) Our analyses applied the revised definition of the primary outcome based on a protocol change that was approved on 8/14/2019, in which single AA recurrences were sufficient to trigger the primary outcome when identified by a 12-lead or ambulatory reading. This protocol modification waived the requirement for 2 consecutive readings which were positive for AA-recurrence in the case of 12-lead and ambulatory readings, and was implemented so that clinical 12-lead ECGs would be able to identify primary outcome events for patients who had stopped sending their smart-phone readings. This correction applies to Section 2.2.1 of the SAP.
- 2) Our analyses used a 30-day window following ablation as specified in the protocol to define the primary safety outcome rather than 90 days as designated by the SAP in Section 2.2.3. The SAP that was saved on 1/21/2021 had designated 90 days because at that time it appeared to our statistical group that it was not possible to determine if bleeding events occurred prior to 30 days or between 30 days and 90 days. We subsequently determined that it actually was possible to determine if bleeding events occurred prior to 30 days post-ablation, and thus were able to analyze the primary safety outcome using the 30 day window that was specified in the protocol.
- 3) The final sample size was 843 randomized patients rather than the 842 specified in Section 3.3.
- 4) Because there were only two deaths prior to AA-recurrence during the follow-up period, we provide conventional Kaplan-Meier curves to describe the cumulative incidence of AA-recurrence events rather than employing a competing risk framework. This modification had no visually discernable effect on the cumulatively incidence curves presented in the manuscript, and simplified the description of the analyses.